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VOL. 49, No. 5 NEW SERIES OCTOBER, 1942

Some Factors in Prognosis in Carcinoma of the Cervix*

BY

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THIS report is based on the records of 151 patients personally treated for carcinoma of the cervix in the years 1929 to 1937, both inclusive. During the same period a further 7 patients were seen who for various reasons were unfit for treatment. They are occasionally referred to. These 158 patients do not include any of the cases recorded by the author in a previous paper.[1] They are, however, all included in the cases reported, or to be subsequently reported, by the Liverpool Radium Institute in the League of Nations Health Organization's "Annual Report on the results of Radiotherapy in Cancer of the Uterine Cervix."

In all but 2 of the treated cases the diagnosis has been histologically confirmed.

One patient only was treated by Wertheim's hysterectomy, the remainder were treated by radium and deep X-rays. The technique adopted for the application of radium follows that advocated by Heyman. Forty-two milligrams of radium element are inserted into the uterine cavity and two applicators, each containing 42 mgm. of radium element, are placed in the lateral vaginal fornices and held in position by tight packing of the vagina with gauze soaked in 1/1000 flavine emulsion. The

* Received for publication March 15th, 1942.

statement of screenage presents its own problem. For comparative purposes the screenage used is often stated in terms of its platinum equivalent only. This is not satisfactory because different metals transmit the various components of the radiations emanating from any one focus of radium in different amounts. Thus, while a given thickness of silver can be held to be the equivalent of a calculated thickness of platinum as regards the transmission of hard gamma rays, the equivalent of the two metals is different for the transmission of, say, soft gamma rays. It seems best, therefore, to give the screenage in detail, viz., platinum 0.5 mm., silver 1 mm., rubber 1 mm. For hard gamma rays the platinum equivalent of the total screenage may be given as 1.45 mm. The radium is left *in situ* for 22 hours. Two further, exactly similar, applications are made. The second application is made 1 week after the first, and the third 2 weeks after the second. Deep X-ray therapy is commenced 6 weeks after the last radium application. The factors utilized have been 220 k.v. ½ mm. Cu. 2 mm. Al. 60 cms. focal skin distance. The areas treated have been right and left anterior pelvis with right and left posterior pelvis with a 15 × 15 cms. size square applicator; or alternatively one anterior and one posterior field 20 × 20 cms. in size.

Each individual dose has been of 350 r units two or three times a week with two areas being treated each time, until the total skin dosage of 6,000 to 7,000 r units has been given.

Accurate records of the radium dosage employed are available, but those of the deep X-ray dosage are not. Later in the paper a section is devoted to the patients who did not receive full radium dosage as above.

"Follow Up"

As all of the 151 cases have been followed up to December 1940, or to the date of death, it is felt that the methods that have made this possible may be of interest.

At the time of treatment the name and address of the patient's own doctor is recorded and also the names and addresses of two relations or friends of the patient.

When the patient goes home after treatment a suitable date is chosen for a first "follow up visit" about three months from the time of conclusion of treatment. Her name, case number and her doctor's name are entered under that date in a book kept for the purpose and she is given a card telling her the date and place at which she is to report.

Future visits are usually spaced at 3 month intervals for the first 18 months to 2 years, then half-yearly to the 3rd year and annually thereafter. If it is found that progress is unsatisfactory, the time between visits is shortened. At each visit the patient is again given a card stating the date and place of the next visit and her name is re-entered under the appropriate date in the follow up book.

At each session of the Follow Up Clinic the book is examined and, if it is found that a patient has failed to report, steps are at once taken to get in touch with her.

There are obviously available four addresses through which the patient may be reached. The usual practice is to write first to the doctor, if this does not produce any reply, next to the patient herself, and if still no reply, to her friends. Should there be no response to any letters, the Almoner of the hospital is asked to visit the last known address of the patient and try to get particulars. If it is learnt that a patient has become bedridden and been admitted to a Municipal Hospital, contact is established as soon as possible with the Medical Superintendent and a request made for information of further progress. This has always been readily and fully given. In cases of special difficulty we have enlisted the aid of the Personal Service Society and the Almoners Department of the Merseyside Hospitals Council. Both organizations have rendered valuable assistance.

The result of this "follow up" has been:

111 patients followed to date of death.

40 patients followed from date of treatment to December, 1940, by visits and reports.

The factors to which I have given attention in an attempt to estimate the prognosis in carcinoma of the cervix may be summarized thus:

I. Factors Concerned with the Assessment of the Local Extent of the Disease at the Time of Treatment.

1. Stage of the growth: League of Nations classification.
2. Cystoscopic appearances.
3. Sigmoidoscopic appearances.

II. Variation in Radium Dosage.

III. Factors Concerned with the Degree of Activity of the Growth.

4. Histological appearances.
5. Colloidal vanadate reaction (modified Bendien reaction).

IV. Personal Factors.

6. Age of patient at time of treatment.
7. Number of children.
8. Duration of symptoms prior to treatment.
9. Coitus after treatment.

V. Special Factors.

10. "Stump" carcinoma.
11. Appearance of disease in relation to pregnancy.

I. Factors Concerned with the Assessment of the Local Extent of the Disease at the Time of Treatment

1. *Stage of the Growth: League of Nations Classification.*

These patients were seen and their "stage" decided according to the 1929 League of Nations classification. The 1929 definitions of the stages were as follows:

Stage 1.

The growth is strictly limited to the cervix uteri. Uterus mobile.

Stage 2.

Lesion spreading into one or more fornices with or without infiltration of the parametrium adjacent to the uterus, the uterus retaining some degree of mobility.

Stage 3.

(*a*) Nodular infiltration of the parametria on one or both sides extending to the wall of the pelvis, with limited mobility of the uterus or massive infiltration of one parametrium with fixation of the uterus.

(*b*) More or less superficial infiltration of a large part of the vagina, with a mobile uterus.

(*c*) Isolated metastases in the pelvic glands, with a relatively small primary growth.

(*d*) Isolated metastases in the lower part of the vagina.

Generally speaking, all cases not falling into Stages 2 or 4 will be placed under Stage 3.

Stage 4.

(*a*) Cases with massive infiltration of both parametria extending to the walls of the pelvis.

(*b*) Carcinoma involving the bladder or rectum.

(*c*) The whole vagina infiltrated (rigid vaginal passage), or one vaginal wall infiltrated along its whole length, with fixation of the primary growth.

(*d*) Remote metastases.

TABLE I
STAGE 1

Year	Number of patients treated	Alive without recurrence							
		3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
1929	0	0	0	0	0	0	0	0	0
1930	2	2	1	1	1	1	1	1	1
1931	2	2	2	2	2	2	2	2	–
1932	2	2	2	2	2	2	2	–	–
1933	1	0	0	0	0	0	–	–	–
1934	2	1	1	1	1	–	–	–	–
1935	4	1	1	1	–	–	–	–	–
1936	4	4	4	–	–	–	–	–	–
1937	13	8	–	–	–	–	–	–	–
Total	30	20	–	–	–	–	–	–	–

SUMMARY:

Number of patients treated 5 or more years ago 13

Of these there are { alive for 3 years ... ... 8 = 61.5 per cent
alive for 5 years ... ... 7 = 53.8 per cent

Total number of cases (1929-37) 30

Of these there are alive:

(1) For 3 years ... ... 20 = 66.6 per cent

(2) Now 3 or more years after treatment 19 = 63.3 per cent

TABLE II
STAGE 2

Year	Number of patients treated	Alive without recurrence							
		3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
1929	2	0	0	0	0	0	0	0	0
1930	4	2	1	1	1	1	1	1	1
1931	9	3	3	2	2	2	2	2	–
1932	3	1	1	0	0	0	0	–	–
1933	4	3	2	2	2	2	–	–	–
1934	3	2	1	1	1	–	–	–	–
1935	7	1	1	1	–	–	–	–	–
1936	11	6	5	–	–	–	–	–	–
1937	9	2	–	–	–	–	–	–	–
Total	52	20	–	–	–	–	–	–	–

SUMMARY:

Number of patients treated 5 or more years ago 32

Of these there are { alive for 3 years ... ... 12=37.5 per cent
alive for 5 years ... ... 7=21.9 per cent

Total number of cases (1929-37) 52

Of these there are alive:

(1) For 3 years ... ... 20=38.5 per cent

(2) Now 3 or more years after treatment 14=26.9 per cent

TABLE III

STAGE 3

Year	Number of patients treated	Alive without recurrence							
		3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
1929	2	0	0	0	0	0	0	0	0
1930	6	3	3	3	2	2	2	2	2
1931	2	0	0	0	0	0	0	0	–
1932	4	0	0	0	0	0	0	–	–
1933	5	2	2	2	1	1	–	–	–
1934	5	1	0	0	0	–	–	–	–
1935	10	5	3	3	–	–	–	–	–
1936	12	1	1	–	–	–	–	–	–
1937	8	0	–	–	–	–	–	–	–
Total	54	12	–	–	–	–	–	–	–

SUMMARY:

Number of patients treated 5 or more years ago 34

Of these there are { alive for 3 years ... ... 11=32.4 per cent
alive for 5 years ... ... 8=23.5 per cent

Total number of cases (1929-37) 54

Of these there are alive:

(1) For 3 years ... ... 12=22.2 per cent

(2) Now 3 or more years after treatment 7=13.0 per cent

TABLE IV

STAGE 4

Year	Number of patients treated	Alive without recurrence							
		3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
1929	0	0	0	0	0	0	0	0	0
1930	3	1	0	0	0	0	0	0	0
1931	2	0	0	0	0	0	0	0	–
1932	1	0	0	0	0	0	0	–	–
1933	1	0	0	0	0	0	–	–	–
1934	2	0	0	0	0	–	–	–	–
1935	1	0	0	0	–	–	–	–	–
1936	3	0	0	–	–	–	–	–	–
1937	2	0	–	–	–	–	–	–	–
Total	15	1	–	–	–	–	–	–	–

SUMMARY:

Total number of cases, 15
Of these 1 lived for 3 years = 6.6 per cent
There are now alive, 0.

TABLE V

STAGES 1 to 4

Year	Number of patients treated	Alive without recurrence							
		3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
1929	4	0	0	0	0	0	0	0	0
1930	15	8	5	5	4	4	4	4	4
1931	15	5	5	4	4	4	4	4	–
1932	10	3	3	2	2	2	2	–	–
1933	11	5	4	4	3	3	–	–	–
1934	12	4	2	2	2	–	–	–	–
1935	22	7	5	5	–	–	–	–	–
1936	30	11	10	–	–	–	–	–	–
1937	32	10	–	–	–	–	–	–	–
Total	151	53	–	–	–	–	–	–	–

SUMMARY:

Number of patients treated 5 or more years ago 89

Of these there are { alive for 3 years ... ... 32=36.0 per cent
alive for 5 years ... ... 22=24.7 per cent

Total number of cases (1929-37) 151

Of these there are alive:

(1) For 3 years ... ... 53=35.0 per cent

(2) Now 3 or more years after treatment 40=26.5 per cent

TABLE VI

	Treated over 5 years ago		Whole series		
	Number	Alive at 5 years (per cent)	Number	Alive at 3 years (per cent)	Alive at 3 years or more (per cent)
Stage I ...	13	53.8	30	66.6	63.3
Stage II ...	32	21.9	52	38.5	26.9
Stage III ...	34	23.5	54	22.2	13.0
Stage IV ...	10	—	15	6.6	—

Tables I to IV record the results in each stage of the disease separately, and Table V gives the results for the whole series.

Reference to Table V shows that the 5-year cure rate for all stages is 24.7 per cent. As the comparable figures for all cases reported by the Liverpool Radium Institute in the third volume of the League of Nations "Annual Report on the results of Radiotherapy in Cancer of the Uterine Cervix" (page 72) is 23.5 per cent, it is claimed that this series is representative of the larger one.

It is generally accepted that this method of staging is a good index of prognosis.

The series here recorded shows an apparent anomaly in that the 5 year survival rate is greater in Stage III than in Stage II (see Table VI). This may be due to an error in allocation of cases to stages or to the number in each group being too small. The figures for the whole series suggest that the latter explanation is probably correct. These figures show that the survival rate for 3 years and that for 3 or more years is in descending order from Stage I to Stage IV.

In the remainder of this paper "alive" is used to mean alive for 3 years or more from treatment.

2. *Cystoscopic Appearances.*

There are records of cystoscopy for 137 patients; almost all these were examined in this way on more than one occasion.

The examination was carried out personally. It was undertaken before a detailed bimanual examination was made to decide the extent of the disease for classification under the League of Nations Stages.

The findings recorded in the present series confirm the suggestions made in an earlier paper[1] that the appearances seen may be placed in the following order as the growth approaches nearer and nearer to the bladder mucosa.

1. Bulging of the bladder floor. (Due to bulk of growth only.)
2. Circulatory changes—i.e. dilatation of vessels (including varicose veins), appearance of new vessels, petechial submucous haemorrhages and definite haemorrhagic suffusion.
3. Transverse ridging.
4. Oedema, in two forms: (*a*) diffuse; (*b*) bullous.
5. Desquamation.
6. Malignant invasion: (*a*) ulcerative; (*b*) hypertrophic.

The findings in 130 patients have been tabulated in two ways.

TABLE VII

Cystoscopic findings	Number	Stages			
		I	II	III	IV
No changes	43	13	15	14	1
Minor changes	45	13	16	14	2
Transverse ridging	14	3	3	6	2
Oedema	28	1	10	9	8

Table VII shows the cystoscopic appearances seen and the stages in which those patients were grouped. It will be noted that in those cases in which no changes or minor changes were seen they were classified mainly in Stages I, II, and III.

Transverse ridging is seen nearly equally in all four stages, while oedema is seen mainly in Stages II, III, and IV.

Conclusion. The more serious appearances in the bladder are found in association with the more extensive stages of the disease.

A table has been compiled to compare the cystoscopic appearances, stage and survival rate (Table VIII).

TABLE VIII

Cystoscopic appearances	Stage I			Stage II			Stage III		
	Number	Alive	Per cent alive	Number	Alive	Per cent alive	Number	Alive	Per cent alive
No changes and minor changes	26	20	76.9	31	7	22.6	28	4	14.3
Transverse ridging and oedema ...	4	2	50	13	4	30.8	15	1	6.6

It would be unsafe to draw any definite conclusions from these figures because those for Stage II do not agree with those for Stages I and III. The latter suggests that the more serious cystoscopic appearances are accompanied by a survival rate below that for the stage of the disease as a whole. It is therefore suggested that the cystoscopic appearances should be taken into account, as well as the findings on bimanual examination, when allocating a particular case to a Stage in the League of Nations Classification. Clearly, if a Stage I case shows advanced bladder changes such as transverse ridging and oedema, the growth is in fact not wholly confined to the cervix and therefore should not be placed in Stage I.

Table IX is compiled to show the relation between the cystoscopic findings and the progress of the patients.

TABLE IX

Cystoscopic findings	Alive			Died			
						Statistical considerations	
	Number	Total number	Per cent	Total number	Average time to death in months	Probable error in average	Standard deviation
No changes	43	14	32.5	29	20	2.075	16.57
Minor changes ...	45	17	37.7	28	24	2.17	17.02
Transverse ridging ...	14	2	14.3	12	26	2.89	14.84
Oedema	28	5	17.8	23	14	2.12	13.09

This shows that the survival rates of patients with transverse ridging or oedema is roughly half that of patients with no changes or minor changes.

This has been tested statistically by comparing the difference in survival rate of the two groups with the standard error of the

difference. Since the difference is about two and a half times its standard error it may be regarded as probably significant.

Table IX also shows the average duration of life in months, of patients, from the time of treatment to death. Clearly the cystoscopic appearances can reflect only one factor of the various ones which combine to produce a fatal result, and, further, the exact site in the cervix where the growth commences will largely determine whether it is likely to spread towards the bladder or not. Table IX shows that the cystoscopic appearances are not an index of the length of expected life. A statistical test shows that there is no significant difference in the average life of patients with "no changes" and those with oedema.

Conclusions. (1) The more serious cystoscopic appearances are associated with a higher death rate.

(2) They are no index of the expectation of life in the cases which are to prove fatal.

(3) Cystoscopic appearances should possibly be taken into account when deciding to which stage a particular case should be assigned. This is especially applicable to cases which are considered clinically to belong to Stage I.

Special cases. There are the further 7 cases out of the total of 137 which could not be included in the above summary because their appearances are specialized.

One patient showed an opaque nodule in the bladder base. She is alive and well 10 years later. One patient who showed marked trabeculation of the bladder base lived 45 months. Another showed a deep pouch in the retrotrigone and lived 20 months. Mock and Dore[2] consider this pouching to be of bad prognostic import. A patient who showed a patch of exudate on the bladder base lived 9 months. The remaining 3 patients showed actual malignant invasion of the bladder; one of these lived 6 months and the other 2 each lived 2 months.

Malignant invasion of the bladder was also found in 3 of the untreated cases; one lived 2 months, and the other 2, one month each. One untreated case showed very gross oedema. She only lived one month.

3. *Sigmoidoscopic Appearances.*

Examination with a sigmoidoscope was carried out on 63 patients at the same time as the cystoscopic, and, consequently, under the same conditions. This number is smaller than that for cystoscopic examination because sigmoidoscopy was given up at the end of 1935 as the author had formed the general im-

pression that it was of no value. A careful and detailed survey of the records of these cases for the preparation of this paper has, however, brought to light some interesting facts.

Not any abnormalities were discovered by sigmoidoscopy in any of the Stage I or Stage II cases. This, of course, is as it should be. One would not anticipate involvement of the rectum in early cases because the bowel is separated from the cervix by the pouch of Douglas.

There are 24 Stage III cases. Fifteen of these showed no changes, of whom 4 (26.6 per cent) are alive. Nine showed various changes, of whom only 1 is alive (11.1 per cent).

The changes found were:

Ridge of growth felt by instrument, 5; Rigidity and fixation of rectal mucosa, 3; Patch of purulent exudate, 1.

Probably the first two groups of changes could have been determined by simple digital rectal examination, but there are no records in the notes of such observations having been made.

Table X shows the duration of life in fatal cases.

TABLE X

Results of sigmoidoscopy	Total number	Average life in months	Probable error in average	Standard deviation
Fatal cases, showing no changes	11	33	4.46	21.96
Fatal cases, changes present	8	12	1.69	7.09

These figures show, as was to be expected, that approach of growth to the rectum affects the prognosis adversely.

The difference in average length of life between the cases which do and those which do not show changes is 21 months with a standard error of 6.13 months. Since this difference is between three and four times its standard error it may be certainly treated as significant.

As there were only 9 Stage IV cases, of whom 1 showed changes, the figures are too small for analysis.

Conclusions. (1) Sigmoidoscopy has given information in Stages III or IV cases only.

(2) The changes noted by sigmoidoscopy were few and possibly digital rectal examination would have given information similar to that obtained by using a sigmoidoscope.

(3) Approach of the growth towards the rectum is of serious prognostic import and affords some information of expectation of life.

II. Variation in Radium Dosage

In the series of 151 cases, 43 patients received less than the standard dosage of radium for various reasons.

The series can then be divided into two groups.

Group A—completely treated—108 patients, of whom 33 are alive 3 or more years after treatment.

Group B—incompletely treated—43 patients, of whom 7 are alive 3 or more years after treatment.

Group B is too small to be divided according to the Stages of the disease for more detailed study, but Table XI sets out the reasons for the departure from the standard technique, the Stages of the individual cases and results.

When the survival rates of Groups A and B are tested statistically no significant difference can be found between them. This is a surprising result, but Table XI shows that the 2 patients who had one application only were both in Stage IV and a fatal result was therefore inevitable. Consequently the patients who survived received two full or three partial applications. Heyman has expressed the opinion that three applications is possibly unnecessarily heavy dosage and in 1930[3] recorded a series of cases treated with two applications only. In that series the survival rate was approximately the same as in an earlier series treated with three applications. The results here recorded, then, tend to confirm Heyman's 1930 paper. The implications for the shortening in time of treatment and the use of a limited stock of radium for a greater number of patients are so important that this question demands further study.

III. Factors Concerned with the Degree of Activity of the Growth

4. *Histological Appearances.*

The relation between histological appearance and prognosis is not so easily assessable as one might infer from Webb-Johnson's[4] recent address, and it is open to question whether this factor is of much practical value. In the first place it is difficult to obtain a completely representative piece of growth from the living patient, and, secondly, although the histological appearances indicate the degree of differentiation of the tumour it is doubtful whether they afford any reliable evidence on which to base the clinical outlook. With regard to the usual technique by which a small piece of material is obtained from the growth by biopsy, Martzloff[5] states that about one-third of the material ob-

TABLE XI

Reason for departure from standard techniques	Stages I	II	III	IV	Dead	Alive
One application only						
Cystoscopic appearances worse when second application was due				2	2	
Two applications only						
Cystoscopic appearances worse when third application was due		1			1	
			1		1	
				1	1	
Persistent temperature after second application	1					1
		1			1	
			1		1	
				1	1	
Patient refused third application		2			2	
			1		1	
Treatment stopped on account of anaemia				1	1	
Mechanical difficulty in application				1	1	
Three applications but incomplete at one or more						
Cystoscopic appearances worse ...		1			1	
			2		2	
				2	2	
Uterine canal not found on one or more occasions		2				2
			6		6	
				1	1	
Lack of available room in vagina	1				1	
		3			2	1
				1	1	
Tear in vaginal wall	1					1
Reduced length of uterine canal	1				1	
		1			1	
Reduced quantity of radium available		1				1
			2		2	
False passage made by uterine sound			1		1	
Severe vaginal reaction		1			1	
No reason recorded	1					1
				1	1	

tained in this way will fail to indicate correctly the predominant variety of cancer cell in the parent tumour. Chambers[6] of the Marie Curie Hospital and Wetterdal[7] of the Radium Hemmet, Stockholm, have also drawn attention to the unreliability of biopsy material, and Forsdike,[8] writing some 10 years earlier, expressed the same view. It is, of course, possible to determine the degree of differentiation displayed by the cells of the growth and it has been shown conclusively that differentiation is related to radio-sensitivity . . . the more highly differentiated the cell the more radio resistant it is, and conversely, the more dedifferentiated, the more radio-sensitive. It might therefore be expected that histological examination would be of use in the choice of treatment and that it should throw some light upon the immediate response of the patient, but most clinicians as well as physicists will agree with Maliphant[9] when he says that in his series of cases though the cytological examination of the tumour would have supplied some information with regard to its immediate response to radiation, it would not have been of any assistance in arriving at the ultimate prognosis. Other authorities take an even more restricted view of the value of histological grading—Jorstad and Auer,[10] for example, stating: " (histological) grading is of no prognostic value. Grading is, or may be, of great value in the radium treatment of a specific case . . . furthermore, it may be the deciding factor in the decision to employ surgical treatment rather than radiation or vice versa." Nevertheless, in spite of these strictures, all the available material from the present series of 151 cases has been re-examined with the intention of testing once again the prognostic value of histological classification. It has already been stated that there is no histological material from 2 patients. Various methods of classifying the histological appearances have been described from time to time, but the principle underlying all of them is the degree of differentiation or anaplasia in the growth. The columnar celled tumours must, of course, be placed in a separate group. In the results now to be described the presence or absence of keratinization has been taken as a simple method of assessing differentiation and the specimens have accordingly been divided into the following groups:

1. Keratinization present.
   (*a*) with cell nests; (*b*) without cell nests.
2. Keratinization absent.
3. Columnar celled growths.

Every section showing evidence of keratinization, however small the area, has been included in group 1.

It should be noted that all the material has been obtained by biopsy and that the results are subject to the limitations imposed by this method.

TABLE XII

Histology of growth	Total	Alive	Percentage alive
Keratinization present:			
With cell nests	11	1	9.09
Without cell nests	52	17	32.7
Total with keratinization	63	18	28.5
Keratinization absent	69	17	24.6
Columnar celled	17	6	35.3

From Table XII it would appear that where the growth shows cell nests the prognosis is much worse than in any of the other types of growth, but when the difference in survival rates of those with and those without cell nests is submitted to statistical test it is found to be of doubtful significance. For this reason and because the number of cases showing cell nests is so small, all cases showing keratinization, in any form, are considered together in the remainder of this section.

Examination of the figures for the three groups—(1) all growths showing keratinization: (2) growths without keratinization, and (3) columnar celled growths, seems to show that the prognosis varies very little and a statistical test of the figures shows that the differences in them are without significance.

The high proportion of cases of the columnar celled type is unusual and may be due to the small total number of cases.

All the sections showing cell nests were derived from cases placed clinically in Stages II and III. This discovery led to the preparation of a special table (Table XIII) which shows the relation between the histology of the squamous celled growths, clinical stage and prognosis. (Stage IV cases are excluded as all the patients died.)

This analysis shows that the percentage survival rate in each histological class in Stages I and II does not differ materially from the survival rate obtained by considering the stage alone.

TABLE XIII

		No. of cases	Alive	Percentage survival rate from histology	Percentage survival rate by stage of growth*
Stage I	Keratinization present†	12	8	66.6	63.3
	Keratinization absent	14	9	64.3	
Stage II	Keratinization present	18	4	22.2	26.9
	Keratinization absent	22	6	27.3	
Stage III	Keratinization present	29	6	20.7	13.0
	Keratinization absent	23	2	8.7	

* See Tables I, II, and III.

† Keratinization present, here = total of those with and without cell nests.

In Stage III, however, we have the apparent anomaly that when keratinization is present the prognosis is better than when it is absent, but statistical test shows that the difference is without significance.

Conclusion. Histological classification of growths, from material obtained by biopsy, is of no assistance in determining prognosis.

5. *The Colloidal Vanadate Reaction.*

This reaction, commonly called the Bendien reaction, has been the subject of much controversy. Our own findings are here recorded, but the full results and the details of the investigation on which they are based have recently been published elsewhere.[11]

Forty-four of the series of 151 cases had repeated estimations of this test performed during periods ranging from just over 1 to 8 years after treatment.

The amount of blood required for the test is 5-10 c.c. This is drawn off with aseptic precautions into a dry sterile test tube, taking care to avoid haemolysis. The serum obtained is tested with a series of dilutions of sodium ortho-vanadate. The dilu-

tions are 20, 21, 22 . . . 30 c.c. of decinormal sodium ortho-vanadate made up to a volume of 200 c.c. with decinormal acetic acid.

The weakest solution which gives a precipitate with the serum is noted. This gives the reading for the test and it is recorded as 21 or 22 etc., according to the amount of sodium ortho-vanadate contained in the testing solution.

Twenty-three of these 44 patients are living. A composite graph of the readings for these 23 survivors is given in Fig. 1. It is made up of 164 observations. In this graph the vertical component records the strength of colloidal vanadate solution used and the horizontal component records time. Each square horizontally represents 1 month and the vertical lines divide the graph into 3 month periods for convenience. The observations for each patient are plotted on to the graph reading from the left end which marks the beginning of treatment. The graph is a practically straight line. It will be noted that there are only 5 readings above 28 and only 6 below 25.

Fig. 2 is a similar composite graph for the 20 patients who have died. It is made up of 107 observations. The graph is composed in the same way as Fig. 1, but the right end is used to mark the date of death for each case and the observations are plotted, as it were, backwards from this date. In this case the graph begins to fall about 2 years before death and falls very steeply in the last year of life. During the last year there are 29 readings below 25, and of these 24 readings are 23 or under.

There is one other case the graph of which is similar to Fig. 2, but although the patient is very ill she has not yet died and so cannot be included in the composite graph.

Conclusions. (1) For patients who remain free from recurrence we have found the colloidal vanadate reaction to lie in a zone between 25 and 28, and, when plotted out, to produce a graph with a practically flat trajectory.

(2) With regard to patients who are doing badly we have found this reaction to have a value below 25 (many of them were in the region of 23 or less) and to produce a graph with a falling trajectory.

Pre-treatment colloidal vanadate reaction. Samples of blood were collected from 65 patients before treatment was commenced. For 38 patients the reading was 25 or over and of these 15 (39 per cent) are alive without recurrence, whereas of 27 patients

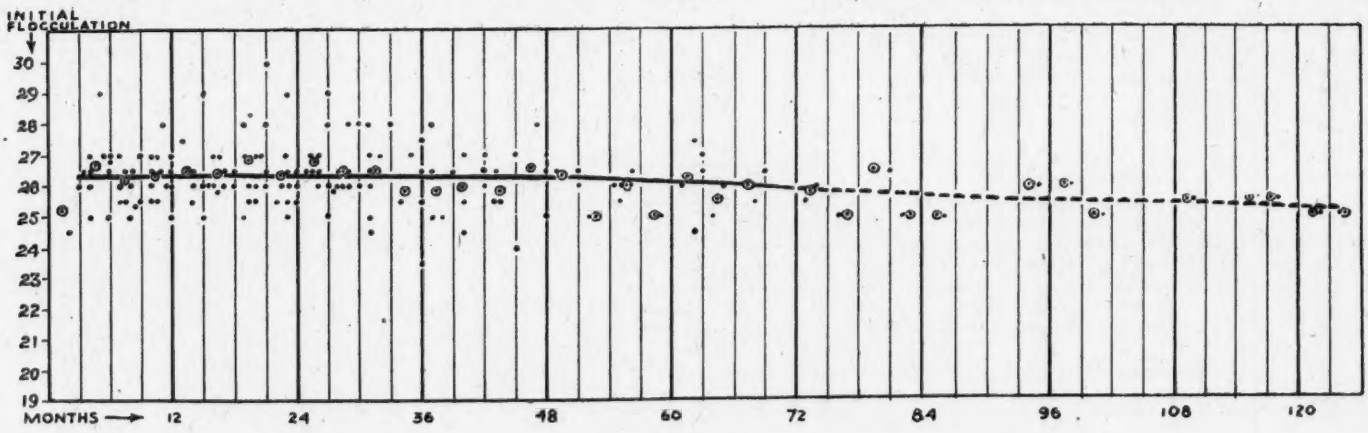

FIG. 1

• Each individual test reading.

⊙ Average reading of the vertical column in which it occurs. From these averages the graph line is drawn.

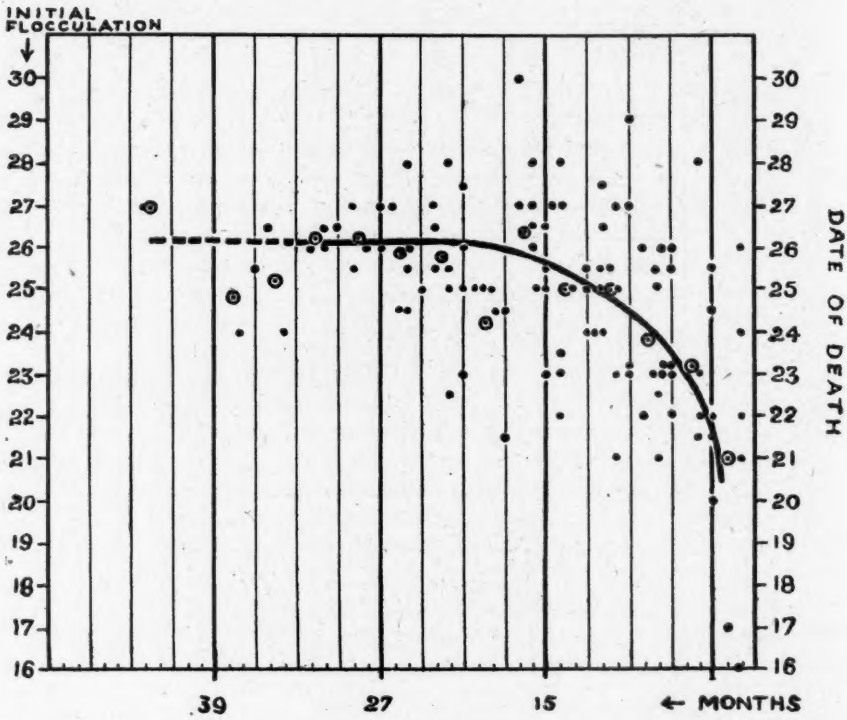

FIG. 2

• Each individual test reading.

⊙ Average reading of the vertical column in which it occurs. From these averages the graph line is drawn.

who had a reading below 25 only 4 (16 per cent) are alive. This difference in proportion is roughly two and a half times its standard error and the first group may therefore be taken as having in all probability a significantly higher survival rate than the second.

IV. PERSONAL FACTORS

6. *Age of Patient at Time of Treatment.*

Table 14 sets out the ages of the 151 treated patients. It gives the survival figures of these age groups and an analysis by stages where the figures are large enough.

TABLE XIV

Age	Number	Percentage of complete series	Survive		Stages				Percentage of combined stages III and IV
			Number	Percentage of age group	I	II	III	IV	
25-30	2	1.3	0						
31-35	4	2.6	3						
36-40	9	5.9	2						
41-45	19	12.5	5*	26.3	6	3	8	2	52.6
46-50	26	17.2	8	30.8	2	13	10	1	42.3
51-55	35	26.1	7	20.0	8	6	17	4	60.0
56-60	22	14.5	10	45.5	3	7	11	1	54.5
61-65	22	14.5	5	22.7	8	7	4	3	31.8
66-70	9	5.9	0						
71-75	3	1.9	0						

* And 2 with recurrence.

The table shows a maximal incidence of the disease at the age group 51-55 and a rising survival rate up to the age group 56-60, except for a break at 51-55. The only factor which might explain this low survival rate in the 51-55 group is that in this group the percentage of Stages III and IV is at its highest; but, on the other hand, the survival rate in the 56-60 group is higher than that in the 46-50 group, although its percentage of Stages III and IV is also higher.

Larger series of figures for complete 5 year survival periods have been reported. They are recorded graphically in Fig. 3. The percentage of survival in each age group is charted (plotted at the nearest whole number). The figures from this series are shown in the continuous line graph. Kimborough and Norris's[12] figures are plotted by the dotted line; Martzloff's[13] by the series of crosses, and Healy and Frazell's[14] by the alternating dot dash line. The last named are shown on the dividing lines in the centre of a decade as they are recorded in 10 year periods.

This figure would appear to show that the decade 50-60 has the best prognosis. This was further tested for the author's cases by comparing the difference between the survival rate of one quinquennium and that which follows it, with the standard error of the difference. The result showed that in no case was there any significant difference. On the assumption that the lack of significance might be due to the small size of the samples, composite figures were prepared.

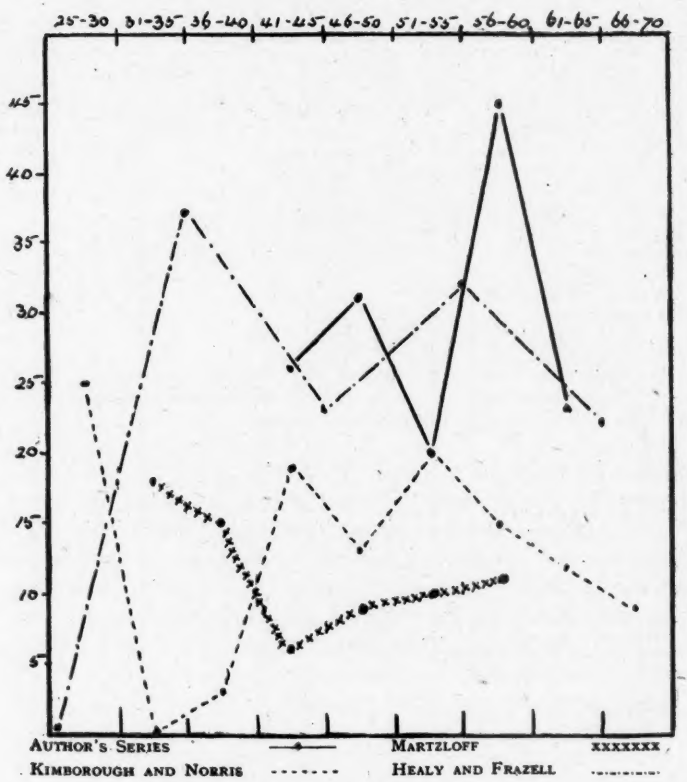

FIG. 3

TABLE XV

Age group	Source	No. of cases	No. of survivals
30–40	Author's series	13	5
	Healey and Frazell	85	32
	Martzloff	110	16
	Total	208	53
40–50	Author's series	45	13
	Healey and Frazell	159	37
	Martzloff	135	10
	Total	339	60

TABLE XV (*continued*)

Age group	Source	No. of cases	No. of survivals
50–60	Author's series	57	17
	Healey and Frazell	183	59
	Martzloff	89	10
	Total	329	86
60–	Author's series	31	5
	Healey and Frazell	100	22
	Total	131	27

Again, if the difference between the survival rate of a decade and that which follows it is compared with the standard error of the difference it will be found not to have statistical significance.

Conclusion. The age of the patient at the time of treatment is not a guide to prognosis.

7. *Number of Children.*

The patients are grouped in Table XVI according to the number of children born to them. Their survival rate and the average length of life of those who have died have been calculated for each group.

TABLE XVI

Number of children	Total cases	Alive		Died			
		Number	Per-centage	Number	Average time to death in months	Probable error in average (months)	Standard deviation
0	18	7	38.8	11	16	1.4	8.8
1	25	7*	28	18	21	2.32	17.22
2	15	6	40	9	33	3.59	20.64
3	15	3	20	12	15	1.89	10.89
4	19	4	21	15	18	2.59	16.78
5	15	4	26.6	11	26	3.6	20.66
6	15	4	26.6	11	14	1.5	8.63
7	6	2	33.3	4	24	4.73	17.19
8	6	2*	33.3	4	29	2.37	8.63
9	6	1	16.6	5	24	4.79	17.42
10	5	–	–	5	19	3.7	12.28
11	3	2	66.6	1	–	–	–
12	2	–	–	2	–	–	–
13	1	–	–	1	–	–	–

* One with known recurrence.

It will be seen that the prognosis of carcinoma of the cervix cannot be related to the number of children born to the patient and that repeated childbearing does not appear to affect the survival time of fatal cases.

As it has been suggested that the total number of pregnancies may be of more importance than the number of actual children born, Table XVII has been prepared in similar fashion to Table XVI.

TABLE XVII

Number of pregnancies	Total cases	Alive		Died			
		Number	Percentage	Number	Average time to death in months	Probable error in average (months)	Standard deviation
0	15	6	40	9	15	1.97	8.78
1	23	8*	34.7	15	23	3.13	17.97
2	14	4	28.5	10	32	4.3	20.18
3	15	5	33.3	10	15	2.17	10.2
4	16	4	25	12	16	2.06	10.58
5	12	3	25	9	26	5.33	23.7
6	16	2	12.5	14	17	2.01	11.16
7	10	1	10	9	17	2.71	12.33
8	3	2	–	1	–	–	–
9	9	2	22.2	7	19	4.05	15.91
10	6	2*	–	4	–	–	–
11	6	1	–	5	–	–	–
12	2	0	–	2	–	–	–
13	1	0	–	1	–	–	–
14	2	1	–	1	–	–	–
15	—	–	–	–	–	–	–
16	1	1	–	–	–	–	–

* One with known recurrence.

This table appears to show a slightly falling percentage of survivals up to and including the fifth pregnancy and thereafter a sharp falling off in survivals. Statistical examination of the figures shows, however, that with the small samples here presented there is no significant difference in the survival rates of the patients who had not been pregnant compared with those who had 6 pregnancies. Further study of Table XVII shows that the number of pregnancies does not give any indication of the expectation of life in fatal cases.

8. *Duration of Symptoms Prior to Treatment.*

It has been stated that the shorter the time between the appearance of symptoms and the receipt of treatment the better the prognosis.

In my experience it is frequently very difficult to assess the time of onset of symptoms caused by the carcinoma. Especially is this so for patients who present themselves at out-patient clinics; some women unconsciously exaggerate their complaints and others minimize them. Moreover, the duration of symptoms, even when accurately known, does not necessarily indicate the duration of the disease.

With these provisos in mind the following results are presented:

The patients in this series were divided into two groups: (1) Those who gave a history of symptoms for 6 months or less and (2) those with symptoms for more than 6 months.

In the first group there are 75 patients, 17 of whom are alive without recurrence, i.e. 22.6 per cent.

In the second group there are 74 patients, 23 of whom are alive, i.e. 30 per cent.

However, when these survival rates are checked by the statistical test employed in other sections it is found that the difference in rates is without statistical significance. Therefore, the duration of symptoms as stated by the patients in this series is of no guide in prognosis.

9. *Coitus after Treatment.*

It would seem that coitus after treatment might have some effect on prognosis. It is well recognized that coitus produces a pelvic hyperaemia and this might possibly be a factor in the production of recurrence.

On the other hand, it must be remembered that a sequel to radium treatment is, almost inevitably, the occurrence of adhesive vaginitis with more or less obliteration of the vagina. When this occurs vaginal drainage is prevented and this, too, might provoke a recurrence.

These ideas have only been recently considered and consequently but few inquiries have been made. The results of these inquiries are here presented without comment. It is intended to make further observations on this matter.

Thirty-one patients have been interviewed and the replies and observations on recurrence are tabulated below (Table XVIII).

TABLE XVIII

Coitus	Number	Non-recurrence	Recurrence	Died
Regular ...	13	12	1	1
Occasional ...	6	5	1*	1†
Abstinence ...	12	11	1	1

* Still alive.

† Died of recurrence in colon.

V. SPECIAL FACTORS

10. *Stump Carcinoma.*

There are 5 cases of carcinoma in the cervical stump following sub-total hysterectomy in this series of 151 cases or carcinoma of the cervix. This is an incidence of 3.3 per cent.

The chief facts about these cases are tabulated below.

TABLE XIX

Case number	Number of children	Years after sub-total operation	Diagnosis at time of sub-total	Stage	Result
148	1	4	Fibroids and appendage disease	I	Recurrence at 28 months*
29	5	12	Appendage disease	IV	Died
82	0	18	Fibroids and appendage disease	II	Died
22	3	20	Fibroids	I	Alive
47	2	22	Not known	II	Died

* This case has already been reported.[11]

It will be noted that all these cases occurred more than 2 years after operation and therefore fall into Nuttall and Todd's[16] classification of "true stump carcinoma."

The survival rate is 20 per cent. The numbers are, of course, too few to generalize upon, but the prognosis is about the same as that for the series as a whole. This is in agreement with Nuttall and Todd's conclusion for "true stump carcinoma."

11. *Appearance of Disease in Relation to Pregnancy.*

In the whole series the disease appeared within 2 years of the last pregnancy in 5 cases. No case occurred during pregnancy. The relevant facts about these patients are given in Table XX.

TABLE XX

Time since last pregnancy	Age	Stage	Alive	Died
3 months	35	I	—	18 months
4 months	44	III	—	12 months
16 months	42	IV	—	20 months
19 months	33	III	7 years	—
24 months	37	IV	—	3 months

Survival rate = 20 per cent.

It will be noted that the 5 year survival rate of 20 per cent does not differ widely from that for the whole series. It would not be wise to draw any conclusions from such a small number of cases. However, the figures—such as they are—do not support the view usually held that the appearance of the disease in close relation to pregnancy make the prognosis unfavourable.

SUMMARY AND CONCLUSIONS

The results achieved in the treatment of 151 cases of carcinoma of the cervix between 1929 and 1937 are recorded.

Various factors in prognosis are considered and an attempt made to assess their value.

1. Stage of the growth: League of Nations classification. This is a valuable index of prognosis.

2. Cystoscopic appearances.

(*a*) The more serious appearances in the bladder are found in association with the more extensive stages of the disease.

(*b*) The survival rates of patients with transverse ridging or oedema is roughly half that of patients with no changes in the bladder or only minor changes.

3. Sigmoidoscopic appearances.

(*a*) Sigmoidoscopy has given information in Stages III or IV cases only.

(*b*) The changes noted by sigmoidoscopy were few and possibly digital rectal examination would have given information similar to that obtained by using a sigmoidoscope.

(*c*) Approach of the growth towards the rectum is of serious prognostic import and affords some information of the expectation of life.

4. Treatment. Variation of the dosage of radium within fairly wide limits does not affect the prognosis.

5. Histological appearances. Histological classification of growths, from material obtained by biopsy, is of no assistance in determining prognosis.

6. Colloidal vanadate reaction. (Bendien reaction.)

(*a*) Observations are made on graphic records of repeated observations of this test during the "follow up" period.

(*b*) Patients who have a low value for this test before treatment have a significantly lower survival rate than those in whom the value is in the normal zone.

7. Age. The age of the patient at the time of treatment is not a guide to prognosis.

8. Number of children and number of pregnancies. These facts about a patient do not form any guide to prognosis.

9. Duration of symptoms prior to treatment. Contrary to expectation this observation was no guide to prognosis in this series of cases.

10. Coitus after treatment. Attention is drawn to this factor, but the available evidence is too small to form any conclusion.

11. Stump carcinoma. The prognosis in true stump carcinoma is approximately the same as when the whole uterus is intact.

12. Appearance of disease in relation to pregnancy. When the disease appears within 2 years of a pregnancy the prognosis is not affected.

13. Statistical testing. In many parts of this paper the value of the figures has been submitted to statistical test. The results, which have been surprising in some instances, seem to emphasize the necessity for such tests whenever attempts are made to draw conclusions from figures.

Acknowledgments

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Degenerative Vulvovaginitis Associated with Oestrogen Imbalance

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INTRODUCTION

THERE is a widespread and deeply rooted belief that post-menopausal pathological conditions must necessarily be associated with low oestrogen levels in the body and, therefore, may usually be benefited by the administration of oestrogens. Yet many such conditions first show themselves long before the cessation of menstruation; moreover, during the years of the "change" there is frequently a functional menorrhagia associated with the same elevated pre-menstrual oestrogen levels as are found in earlier life with most examples of functional menorrhagia. Curettage, either then or after the termination of the menopause, not infrequently reveals an endometrium suggesting unbalanced or unopposed oestrogenic stimulation.[1] There is now a considerable body of evidence [2, 3, 4, 5, 6] to indicate that even long after the menses have ceased at the climacteric the blood and urine may contain considerable quantities of oestrogen, and logical explanations of its origin in the adrenal cortex or anterior pituitary have been proposed.

If such observations mean anything, they imply that certain menopausal and post-menopausal patients are as apt to need less oestrogen as more, and that oestrogen assays should be a necessary preliminary to any rational menopausal therapy. Yet gynaecologists continue to be mesmerized by the *prima facie* credibility of the thesis that at the climacteric there is inevitably ovarian failure leading, in a certain proportion of women, to the appearance of hot flushes, headache, melancholia, obesity, vulvar atrophy and, of course, a permanent amenorrhoea.

McLarern[7] reported that fully 28 per cent of the post-menopausal women studied by him continued to have a normal vaginal flora to even an advanced age, that in this group 15 of

17 women over 70 years of age exhibited normal vaginal smears, that 6 out of 8 vaginal biopsies from such women over 70 years of age displayed a normal epithelium, and that all vaginal biopsies at all ages exhibited glycogen in the epithelial cells. All too rarely one finds a report which emphasizes the percentage of failures encountered in the management of menopausal states by means of oestrogen replacement. However, Lawrence and Moulyn[8] have recently reported 43 per cent of failures in 100 unselected menopause patients so treated, and there are a few similar records[9] in the literature. Such *data* scarcely support the idea of universal oestrogen deficiency after the menopause.

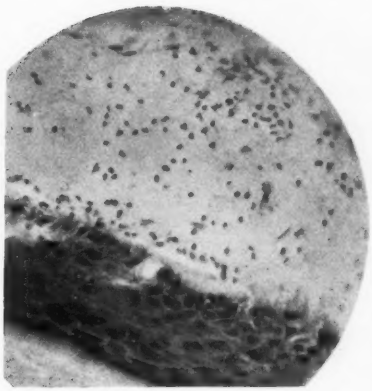
For a number of years the writer has been impressed by the fact that many post-menopausal women continue to have either oestrogen cycles or occasional high levels of oestrogen in the blood. Fluhmann[10] in particular has brought forward strong support for this view. This is somewhat analogous, perhaps, to the continuance of oestrogen cycles during the amenorrhoea of pregnancy[11] or throughout the so-called secondary amenorrhoeas. Urine assays are of doubtful value[12, 13, 14] in determining what goes on in the body's metabolism of oestrogens, and vaginal smears may be poorly correlated with ovarian changes[15]. We have, therefore, made blood assays[16, 17, 18, 19], one of several, upon women at or after menopause having either senile vulvovaginitis or kraurosis vulvae and, or only, severe vulvar pruritus or burning. Table I presents an unselected series of such cases, with especial reference to the striking benefit some of them derive from vitamin E[20], an anti-oestrogen[21].

General Analysis of the Data

Table I summarizes the case histories of 31 women with degenerative vulvovaginitis kraurosis vulvae, or vulvo-vaginal pruritus, all of them private patients. Of these 31 women, 26 were menopausal or post-menopausal and 5 were seen prior to the climacteric. Four were examples of kraurosis vulvae. The vagino-vulvar appearance in the 26 menopausal and post-menopausal women and in cases 14, 22 and 30 of the ante-menopausal group ranged all the way from vaginal redness, vulvar hair loss and labial atrophy, with loss of the usual cutaneous sheen, to whitening of the labia, perineal body and about the anus with or without numerous reddish cracks. This process has even gone on, as has been indicated, to typical kraurosis vulvae, of which the worst example was the youngest patient, aged 25 years.

The writer was unable to correlate the clinical appearance of any of these patients with either the blood oestrogen findings or with the type of therapy which later proved effective. For example, the appearance of the vagina or vulva in the 16 patients cured by vitamin E seemed identical with that of the 7 patients cured by the use of oestrogens, and he could not detect beforehand merely by inspection which women would respond to either or neither medication. The blood oestrogen analyses were helpful in differentiating the cases for appropriate treatment, a point which should be stressed, but there were many difficulties in the way of using them properly. Such patients usually present themselves after many other treatments have been tried and found wanting. They are acutely miserable and desire the earliest alleviation. They resent the suggestion that a proper preliminary study of them entails waiting a month, or some fraction thereof, for periodic oestrogen tests in order to determine the presence or absence of regular oestrin cycles. They have often had oestrogen therapy before they come to a consultant, which vitiates the blood oestrogen analysis for at least 3 to 4 days thereafter. It will be seen, however, that such oestrogen analyses as we were able to secure pointed the way to a suitable type of therapy in 13 cases and were quite unhelpful in 10 cases. Nature, or sedative therapy with or without isolation, cured at least 3, and there is a good possibility that several cures which we have ascribed to the use of oestrogens or vitamin E might have been attained without either. Certainly a psychogenic element is not to be discounted in the consideration of such complaints as vulvar or anal pruritus in which often attendant gross changes are not to be seen. However, it would be equally rash to assign all of our happy results or even any large proportion of them to the suggestive effects of the various medicaments used, because very obvious physical changes in the skin or mucous membranes so often paralleled the patient's report of relief. Excluding the 3 cures fairly ascribable to Nature, cures are claimed in 24 of the 28 women (86 per cent of cures). This is certainly too generous a claim, for too short a period of observation has ensued in many of these cases to assure permanence of relief. What is clear, however, is that at least as many of these patients suffering from senile vulvovaginitis or post-menopausal vulvar pruritus respond to vitamin E as to an oestrogen and that the therapeutic benefit obtained is of surprising duration.

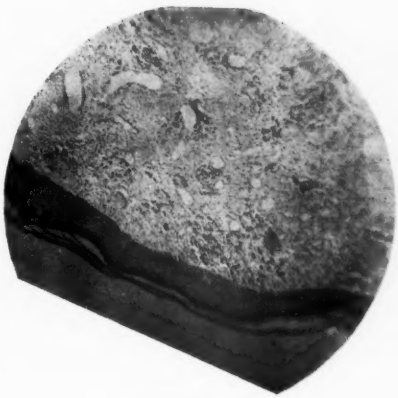
Idiosyncrasy to wheat germ oil has been reported before[23, 24] and is merely called to mind again in passing.

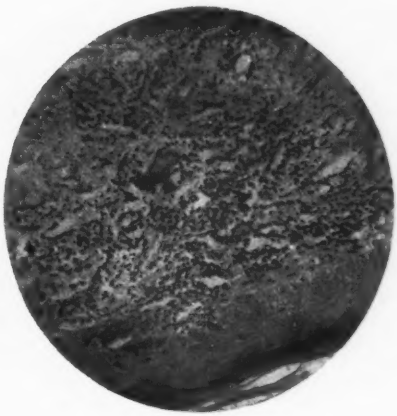


Low Power
June 16th, 1941

High Power
June 16th, 1941

Biopsy From Labium Minorum
Case 30





Low Power
July 4th, 1941

High Power
July 4th, 1941

Biopsy From Labium Minorum
Case 30

E.S. (D.V.)

Degenerative Vulvovaginitis Associated with Oestrogen Deficiency

It may be that relatively few of this type of patient gravitated to the writer because of the general tendency in the profession to treat and heal such cases with oestrogens. However, it is of some significance, perhaps, that only 7 of the 31 cases in Table I were cured by oestrogens and some were actually made worse by their use. This latter point has been mentioned elsewhere[20], in a report of 4 cases of degenerative vulvovaginitis cured by the use of vitamin E. This really means that the percentage of such patients seen by the writer which demanded the use of oestrogens was only 20 per cent.

The clinical improvement in these patients obtained with the use of oestrogens appears rapidly, most women experiencing substantial relief within 3 to 7 days, and the physical appearance of the vagina alters as rapidly; it may even assume a dark violaceous colour, suggesting the intense Chadwick's sign seen in late pregnancy. It is well established that the change is associated with the re-appearance of a multi-layered squamous epithelium in the vagina. The puzzling feature about both this and the high oestrin type of vulvovaginitis is that cures once achieved tend to persist for some time or may even be permanent, although the underlying cause must remain.

Degenerative Vulvovaginitis Associated with Oestrogen Excess

This type of vulvitis or/and vaginitis has a physical appearance identical with that of the low oestrogen type. Therefore, the differentiation is solely by oestrogen assay or the clinical trial of therapeutic opposites. This type may be suspected sometimes, but not always, on the basis of a pre-existing functional menorrhagia or hypothyroidism, which are generally associated with high oestrin phenomena. It constituted 16 of the 31 cases presented here and all 4 in the author's previous paper on the subject—an incidence of 57 per cent. Many of these women had had prior oestrogen therapy or various ointments had been used locally; they had experienced little or no help or had even become worse under such treatment and had come to the writer in desperation. This may not represent, therefore, the true incidence of this type of lesion. But it should be pointed out that

10 of the 17 women (59 per cent) who had not had previous oestrogen or vitamin treatment of any sort required vitamin E for cure, and these two figures coincide closely.

As typical kraurosis vulvae was seen in association with either high or low oestrogen values in the blood and responded to either type of therapy, as indicated by such assay, it would seem that it may be but a late aspect of such senile vulvovaginitis. It can scarcely be a more definite clinical or therapeutic entity than the degenerative vulvovaginitis that has preceded and merged into it.

Therapeutics

Several points in the management of these cases should be stressed. The patients having low blood oestrogen values usually respond quite well to oestrogens given by any route, but, perhaps, do best on suppositories. As has been said, the effect is prompt, developing within a week or two, and lasts for weeks or months or even longer. There is a tendency for the condition to recur—when it responds quite as well as at first to the same therapeutic measures. If oestrogens are used for the high oestrin cases the vulvovaginitis may be aggravated and become very distressing. However, this is not always so, as Table I reveals—indicating either that our qualitative oestrin assay is sometimes fallacious or that such patients are occasionally healed by thickening the epithelium with or without cornification.

In the high oestrin cases the patients need such an anti-oestrogen as thyroid extract or vitamin E. We have not tried such others as progesterone, chorionic gonadotrophin or testosterone propionate. Certain women have an idiosyncrasy to wheat germ oil[22]. These must be given synthetic vitamin E or the alternatives mentioned. The dose used[20] must be enormous. We have usually had to administer as high as 3 ounces of bulk, cold-pressed wheat germ oil (Kelly's) or nearly 100 milligrams of α-tocopherol acetate (Hoffmann-La Roche) per day. This dosage must be continued for 2 weeks as a minimum and perhaps for as long as 6 weeks or even longer before the patient is relieved. A smaller dose is quite unhelpful. The vulva or vagina displays a great degree of healing before the patient experiences any subjective relief. If the histological sections on the case reported offer any indication of the reason for this lag in therapeutic effect it would seem that one must wait until the vascular supply of the locally senile tissues has been restored to a more

normal state. New capillaries take time to grow, and it takes time for inter-cellular deposits to be absorbed and the normal cell architecture of the epithelium and corium to be restored. It is unfortunate that biopsies on only one patient were obtainable, but such was the case, as all were private patients. These women resent the huge doses of vitamin E preparations used, and are apt to give up hope and disappear about the time the physician begins to see the first signs of healing. If one can induce them to persist with the treatment, they soon begin to experience relief thereafter. Some of these women obtained permanent relief. Some relapse and need further courses of treatment. The tissue changes alluded to above may explain the curious phenomenon of the prolonged cure often obtained.

It cannot be denied that a certain proportion of patients suffering from vulvar pruritus are psychogenic and therefore respond to anything or nothing. (*Vide* cases 9, 17, 18, 27, 28). It would be a great mistake to assume that all pruritus cases fall into this group, for in the majority relief is not experienced until the proper treatment is given, and then one soon sees one of the most striking tissue restorations that is to be observed in the whole domain of therapy.

Collective Discussion

It is here contended that the same clinical condition of the external genitalia may be characterized by either positive or negative blood oestrogen values. A point that cannot be stressed too strongly is that senile vulvovaginitis and kraurosis vulvae, like dysmenorrhoea[23] or toxaemia of pregnancy[24], are not single diagnostic entities but evidences of endocrine or other imbalance having differing endocrine correlates. The writer, at least, cannot distinguish between the gross appearance of the various types of such degenerative vulvo-vaginal states, just as he cannot differentiate the clinical types of endocrine dysmenorrhoeas or of early or late pregnancy toxaemias. In all these conditions the profession keeps struggling for a clinical short-cut which will eliminate laboratory assistance—something it does not attempt in diabetes mellitus, for example—and meantime is naïvely disappointed when its flounderings without compass or range-finder lead to frequent therapeutic failures. It should be stated boldly and as a gynaecologic axiom that such conditions require endocrine assays as an essential prelude to diagnosis and proper treat-

ment. One cannot stress that point strongly enough. Short of that we run the grave risk of discrediting endocrine gynaecology for years to come.

It will be noted that, as in our first report, not all of these women with degenerative vulvovaginitis were menopausal or post-menopausal[25]. This may serve to explain the persistence of local distress in certain cases of trichomonas vaginitis, for example, after the parasite has been exterminated. There were 5 complete failures in the series studied. No comment is offered as these were complete, and often unexpected, puzzles to the writer. He could not detect any clinical nor endocrine features of these cases which should have led to an unfavourable prognosis in respect to the methods used.

CASE REPORTS

CASE 8. This woman, aged 54 years, was seen first on July 24th, 1941. She had had vaginal irritation and burning for 3 years before. She had had emmenin with some relief. A prominent gynaecologist had examined her under anaesthesia, then applied local ointments and cold compresses, with suggestive therapy. When the pruritus persisted he had performed a curettage, after which he had applied silver nitrate locally on several occasions, and periodically had dilated the vagina. He told her a vulvectomy might be indicated if kraurosis should develop. She was treated by this physician for about a year and a half, but grew steadily worse.

She had had a thyroidectomy by Dr. Crile in 1925, after the unsuccessful use of radium, and an X-ray menopause in 1938. Her weight had increased 20 pounds since the menopause and a slight hypertension had developed. There were no peri-anal changes and very little vaginitis, but there was a mild, diffuse redness of the minimally indurated labia majora. She wanted immediate treatment, so a blood oestrogen was taken, and she was put on vaginal suppositories of Shering's Progynon—D.H. (2500 units in each). To my surprise the oestrogen was positive, and when she returned on August 2nd she had not experienced any relief, and there was more vulvar induration, with some purplish discoloration. Accordingly, the treatment was changed from the oestrogens to 50 mgm. of Ephynal per day .

On August 9th she felt the same, but the right labium was more pliable. By mistake she had kept on using her suppositories as well as the vitamin E. She stopped the oestrogen therapy now, and returned on the 16th with great improvement. The right labium was nearly healed, but some furnucles had developed in the left labium. A crack in the left labio-crural crease was healing. She felt slightly easier at night. Her dose was raised to 75 mgm. per day. By the 25th there was still much local pruritus but the boils had disappeared and not recurred. There was anal pruritus, too. The vulva was normal in appearance, and all skin excoriations had healed. She said she was " 25 per cent better." By September 5th she said she was " 50

per cent better." She had suddenly lost her husband and her father in the preceding fortnight. She wrote to me on September 22nd that she was cured, and she has remained so.

CASE 12. The patient, aged 76 was first seen on September 4th, 1939. She had had attacks of vulvar burning and itching for 9 years and 5 years before: the present one began July 1st. Her physician had sent in a blood test for oestrogen determination 9 days before I saw her and this had been positive. He had, accordingly, put her on 1½ ounces of Kelly's wheat germ oil per day, obtaining a change in the appearance of the vulva and some symptomatic relief.

When seen she had a very tender vagina without discharge, no pelvic pathological findings, and a healing, dry, injected, roughened vulva and perineum. The peri-anal region was not abnormal in appearance. As she needed more vitamin E, but was unable to take more bulk oil, she was given in addition 108 mgm. of Ephynal (Hoffman La-Roche) per day.

On September 8th she had had 2 days of complete relief. The vulva appeared normal but for one tiny crack. The injection had disappeared and the flesh had become very pliable. There were no more superficial crusts. By October 2nd she was completely cured and has remained so: sending me another such sufferer in the meantime. (Case 15).

CASE 13. This woman, aged 50 years, was seen first on December 20th, 1937. She had not menstruated for the previous 3½ years, and her hot flushes were disappearing. She had been nervous for the past 20 years. There was some leucorrhoea, for which Devegan had been used locally. A "pins and needles" sensation about the anus and perineum was "driving her crazy." Three weeke before she came to me a good surgeon had performed a haemorrhoidectomy for the anal pruritus. There had not been any improvement, however, in the interval.

There was not any pathological findings apart from the pelvic examination. The vaginal mucosa appeared normal and was not tender. The uterus was atrophic and the adnexa were not palpable. The skin of the labia was smooth, pale pink, as was the peri-anal skin, the labia being atrophic and nearly hairless. Weekly blood oestrogens were done. The third one, on January 3rd, was positive. It was thought she was still having cycles, and she was given 1½ ounces of Kelly's wheat germ oil, then 1 dram per day thereafter.

By January 12th the vulvar irritation had almost gone, and the peri-anal distress was distinctly less. Her hot flushes were unchanged. There was a remarkable improvement in the appearance of the vulva. She was told to take 2 drams of oil per day. By the 20th, however, a discrete papular rash appeared on her abdomen, thighs, and the back of her hands. The vulva seemed normal. Her hairdresser remarked that her hair was growing again. It had been falling out rapidly for months before. On February 1st it was obvious that she couldn't tolerate wheat germ oil. She was suffering intense pruritus all over her body and the soles of her feet; and cutting down the dose to 1 dram a day did not decrease this. There

was a fine, general, reddish rash 2 hours after each dose of oil, she noticed. She tried hard to persevere for she " felt generally better than for 5 years." The vulvar skin was soft, pliable, and normal, as was the peri-anal skin. The treatment was changed to thyroid extract, gr. ½ per day. By the 9th she had developed an eczema for the first time in her life. There was excoriation all over her legs, arms, and neck. It was almost a weeping type. A dermatological colleague, Dr. Sexton, cleared up the dermatitis by local applications, and she has remained well since that time on her thyroid medication.

CASE 23. This woman, aged 49 years, first seen on December 9th, 1940, was very wealthy, and very active in many community enterprises. Her life had been made miserable by menorrhagia until a radium menopause had been induced in 1929 by Professor Chipman, of Montreal. For the last 2 years her distress had returned in the form of vulvar burning, which was worse at night. She had had adequate oestrogenic therapy without relief or with even some exacerbation of her complaints; but an alternative had not been suggested to her. She was definitely hypothyroidal, which at once suggested that she was an oestrin-high type. Examination revealed a very red vaginitis with trichomonas infection. The inner aspects of the labia were parchment-like, reddened, and showed petechiae. The peri-anal skin was sensitive, but looked normal. The corpus uteri was free, in second degree retroversion.

She was put on Stovarsol tablets, to be used vaginally. A blood oestrogen test was taken (it was positive) as she had not had oestrogen therapy for the previous 5 days, and she was at once put on 3 ounces of Kelly's wheat germ oil, and 40 mgm. of ephynal per day.

She was cured in 10 days time, was asked to continue her therapy for a time to consolidate her result, but failed to do so. Her pruritus ani recurred on May 1st, 1941. She used her old bottle of wheat germ oil again, being unaware of the rapid deterioration of such oil on standing, even in a refrigerator, and obtained no relief. She was put on fresh oil and Ephynal again, and cleared up as completely and as rapidly as before.

CASE 29. This woman was 56 years old. She was seen first on April 12th, 1941, with a history of vulvar itching for the previous year. A local gynaecologist had recommended hysterectomy as a cure. Local examination revealed an atrophic introitus, the labia minora bleached a dirty, dead, yellowish white, of the nature of kraurosis. There were many characteristic reddish streaks throughout. The cervix had been badly torn years before, the corpus uteri was retroverted third degree, and was slightly enlarged. There had been a history of menorrhagia and other evidences of hypothyroidism remained.

She was put on gr. 1 of thyroid extract. There was slightly less pruritus on April 29th, and the dose was raised to gr. 1½. On the 26th the pruritus was " the worst yet." The vulva, however, looked much better, as the red streaks were disappearing and the whiteness was less marked. She was put on 3 ounces of wheat germ oil per day. By May 10th the pruritus had disappeared and the vulvar lips were pinker without red markings.

On November 29th pruritus was still absent, the vulva was whitish, but was pliable, not tender and did not show any red streaks. She was maintained on her thyroid dosage and has remained well.

CASE 30. This girl was only 25 years old. She was first seen on June 19th, 1941, when her physician became ill. There had been vulvar irritation for the past 2½ years. Since February she had used local ointments and had taken 6 mgm of phytoferrol a day. A biopsy, taken on June 16th, did not bleed, be it noted, and revealed a typical kraurosis vulvae, as the accompanying microphotographs will demonstrate. The clinical picture was classical and unmistakable. There was no vaginitis. She had oligomenorrhoea and dysmenorrhoea, and showed signs of hypothyroidism which had been relieved by thyroid therapy. A blood oestrogen was taken just after the menses, and her treatment was switched from vitamin E to stilboestrol (B.D.H.) 5 mgm. per day The oestrin was positive after her menstruation, so she was taken off the stilboestrol on the 20th and put on 100 mgm. of ephynal per day. On the 28th she looked almost cured, and a normal pink colour was returning. The superficial slough was nearly gone. On July 4th she felt "about 50 per cent improved." A biopsy was repeated immediately adjacent to the last one, on the left labium minorum. It bled tremendously all night and she re-appeared next morning with marked anaemia (62 per cent Sahli), a huge clot covering the vulva and perineum, and required suture to control further bleeding.

Thereafter her condition remained unchanged. She was put to bed for as long as 3 days at a time, and radiant heat applied to dry up the moist vulva. Her work required her to walk all day long and the labia minora, which protruded slightly, tended to be desquamated in patches. She was unable to change her occupation. It was noticed that her condition was worse each month just prior to menstruation, when the level of blood oestrogen should be highest. She had a good result for a time in September, but relapsed thereafter. Large doses of vitamin A were given, in addition to her E therapy, after October 14, but it did not produce any improvement. In fact, on December 3rd her condition was at least as severe as when she had first come under my care. Her physician had now recovered, and the patient was accordingly returned to her care, with the suggestion that X-ray therapy be attempted before vulvectomy was resorted to. The patient showed a preference for operation.

This case has been listed as a failure; but the microphotographs of the two biopsies are of interest in indicating a tissue response to vitamin E. The tissues of the second biopsy reveal less keratinization of the epithelium, a great decrease in the intercellular substance which had nearly obliterated cell architecture in the corium in the biopsy taken just 18 days before, and many more vessels appear in the corium. These may be old vessels re-opened, or new ones which have been developed. The later supposition would account for the invariable time lag between the institution of treatment and the appearance of gross tissue improvement, and subjective relief. The increased vascularity is borne out by the haemorrhage, developing

only after the second biopsy. This tissue regeneration is a striking phenomenon, with interesting physiological and therapeutic implications.

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TABLE I.

Case	Age	Diagnosis	Severity of complaint	Duration of complaint	Blood oestrogen values and number of such determinations	Therapy before seen by the writer	Writer's therapy	Result	Duration of observation since
(1)	50	Vaginitis after surgical castration	+	1 year	Not done	None	Wheat germ oil, Stilboestrol	Failed Cured	2 years
(2)	55	Post-menopausal vaginitis and vulvitis	+ +	3 months	+ (once)	None	Oestrogen suppositories before assay known	Cured	1 year
(3)	60	Post-menopausal vulvitis	+ +	1 year	+ (once)	None	Oestrogen suppositories before assay known	Cured	3 years
(4)	35	Residual vaginitis after trichomonas	+ +	6 months	Not done	Gentian violet and Devegan	 Wheat germ oil	Failed Cured	3 years
(5)	50	Post-menopausal vaginitis	+	1 year	+ (once)	None	Wheat germ oil	Cured	1 year
(6)	51	Post-menopausal vaginitis	+ +	1 year	+ (once)	None	Oestrogen suppositories	Cured	4 years
(7)	63	Post-menopausal vaginitis	+ +	10 years	Test lost	Local ointments	 Oestrogen suppositories, Wheat germ oil, X-rays suggested, but advice rejected	Failed Failed Failed	

TABLE I (*continued*)

Case	Age	Diagnosis	Severity of complaint	Duration of complaint	Blood oestrogen values and number of such determinations	Therapy before seen by the writer	Writer's therapy	Result	Duration of observation since
(8)	54	Post X-radiation, menopausal vulvar pruritus	+ +	3 years	+ (once)	Local ointments, Cold compresses, Curettage		Failed Failed Failed	
							Oestrogen suppositories before assay reported,	Failed	
							Wheat germ oil	Cured	4 months
(9)	58	Post-menopausal vulvitis	+ + +	2 years	Not done	Oestrogen hypos.		Failed	
							None	Cured	4 years
(10)	48	Post menopausal vulvitis	+ + +	1 year	+ (once)	Stilboestrol		Failed	
							Wheat germ oil	Cured	1½ years
(11)	73	Post-menopausal vaginitis and vulvitis	+ + + +	3 months	Not done	None	Wheat germ oil	Cured	2 years
(12)	76	Post-menopausal vulvar pruritus	+ + +	9 years	+ (once)	Wheat germ oil		Helped	
							Huge doses of wheat germ oil	Cured	2 years
(13)	50	Post-menopausal vulvitis	+ + +	6 weeks	One + in 3 tests done a week apart	Haemorrhoid-ectomy	Wheat germ oil	Cured	Severe idiosyncrasy developed
							Thyroid extract	Cured	4 years
(14)	38	Vulvar pruritus	+ +	4 years	Not done	Local ointments, Oestrin X-rays		Failed Helped Failed	
							Wheat germ oil	Cured vulvar pruritus but did not help anal pruritus	3 years

TABLE I (*continued*)

TABLE I (*continued*)

Case	Age	Diagnosis	Severity of complaint	Duration of complaint	Blood oestrogen values and number of such determinations	Therapy before seen by the writer	Writer's therapy	Result	Duration of observation since
(15)	61	Post-menopausal vulvar pruritus	+ + +	1 year	Two negatives in tests done a week apart	None	Oestrogen suppositories,	Worse	
							Wheat germ oil, plus alpha tocopherol acetate	Cured	1 year
(16)	67	Post-menopausal vulvar pruritus	+ + + +	6 years	+ (once)	Rest and sun,		Failed	
						Ultraviolet,		Failed	
						Barbiturates,		Failed	
						X-rays,		Failed	
						Oestrogen suppositories,		Failed	
						Wheat germ oil		Failed	
							Wheat germ oil,	Failed	
							Vitamin A,	Failed	3 years
(17)	58	Post-menopausal vaginitis and vulvitis	+ + + +	2 years	+ (once)	None	Wheat germ oil,	Helped	
							Oestrogen suppositories,	Worse	
							Bed and isolation plus sedatives	Cured	2 years
(18)	26	Vulvar pruritus	+ +	Occ.	+ (after menses)	None	Thyroid extract,	Helped	
							Wheat germ oil	Cured	Often recurs in 3 years past, when under mental strain
(19)	50	Post-menopausal vulvar pruritus	+ +	1 year	− (4 tests a week apart)	Oestrin		Failed	
							Thyroid,	Failed	
							Wheat germ oil	Failed	
							Oestrogen suppositories	Cured	2 years

TABLE I (*continued*)

Case	Age	Diagnosis	Severity of complaint	Duration of complaint	Blood oestrogen values and number of such determinations	Therapy before seen by the writer	Writer's therapy	Result	Duration of observation since
(20)	58	Post-menopausal vaginitis	+ + +	1 year	− (once)	None	Oestrogen suppositories	Cured	2 years then died
(21)	69	Post-menopausal vulvitis	+ + +	4 months	+ (once)	Oestrogen suppositories		Failed	
							Wheat germ oil,	Failed	
							X radiation,	Failed	
							Wheat germ oil	Failed	4 months
(22)	27	Early senile vulvitis	+ + +	1 year	+ (after menses)	Area excised, and leukoplakia diagnosed but not confirmed histologically		Failed	
							Wheat germ oil	Cured	8 months
(23)	49	Post-radiation menopausal vulvar pruritus	+ +	2 years	+ (once)	Stilboestrol		Worse	
							Wheat germ oil	Cured	Recurred in 5 months, but cured again
(24)	47	Condylomata acuminata and vulvar pruritus	+ +	6 months	+ (once)	None	Cauterized condylomata,	Failed	
							Wheat germ oil	Cured	5 months
(25)	48	Post-radiation menopausal vulvar pruritus	+ +	6 years	− (3 tests done a week apart)	Emmenin oestradiol		Helped	
								Helped	Recurred in 12 months
							Wheat germ oil	Cured	Idiosyncrasy to wheat germ oil
							X-radiation	Cured	10 months

TABLE I (*continued*)

Case	Age	Diagnosis	Severity of complaint	Duration of complaint	Blood oestrogen values and number of such determinations	Therapy before seen by the writer	Writer's therapy	Result	Duration of observation since
(26)	45	Post-radiation menopausal vulvar pruritus	++	4 months	Not done	None	Thyroid extract	Cured	6 months
(27)	41	Post-radium menopausal vulvar pruritus	+++	4 years	+ (once)	Oestrogen (hypo) (Suppositories)		Helped	
								Failed	
							Wheat germ oil, X-ray suggested but advice rejected	Failed	
(28)	63	Early kraurosis vulvae	+	6 months	+ (once)	None	Did not return for 25 months, no therapy	Cured	1½ years
(29)	56	Kraurosis vulvae	+++	1 year	+ (once)	Local ointments, hysterectomy advised		Failed	
(30)	25	Severe kraurosis	++++	1 year	+ (after menses)	None	Wheat germ oil	Cured	6 months
							Small doses α-tocopherol acetate plus thyroid,	Failed	
							Huge doses of same,	Failed	
							Vitamin A	Failed	6 months
(31)	54	Kraurosis vulvae	+++	2 months	− (once)	None	Stilboestrol	Greatly improved	6 months' relapses if therapy ceased

Because anal pruritus is occasionally associated with vulvar pruritus of this type, the following few cases are added for their general interest

TABLE II

Case	Age	Diagnosis	Severity of complaint	Duration of complaint	Blood oestrogen values and number of such determinations	Therapy before seen by the writer	Writer's therapy	Result	Duration of observation since
(1)	33	Anal pruritus	+++	2 years	+ (on many occasions)	None	Wheat germ oil	Cured	Recurs each winter, and cured each year for 4 years past by taking wheat germ oil throughout winter and spring
(2)	31	Anal pruritus	+++	2 months	Not done	None	Wheat germ oil	Cured	Three years then recurred and cured again
(3)	37	Anal papilloma and anal pruritus	++	1 year	+ (after menses)	None	Papilloma removed, Thyroid extract	Same Cured	6 months
(4)	29	Anal pruritus	+++	6 months	Not done	None	Wheat germ oil	Cured	3 years
(5)	37	Anal pruritus	++	3 months	+ (once, taken after X-ray castration)	None	Wheat germ oil	Cured	3 years

Erythroblastosis or Congenital Syphilis? Observations on Erythroblastosis and its Differential Diagnosis from Congenital Syphilis

BY

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ERYTHROBLASTOSIS is a common foetal and neonatal disease which is still not generally recognized. It is proposed to outline the clinical and pathological features, paying more attention to the graver forms and, particularly, to emphasize the close resemblance of the latter to congenital syphilis.

During the last 5 years, I have observed a series of 53 infants with erythroblastosis. My paediatric appointment at a maternity hospital has enabled me to observe closely 30 of the series from birth. This has been a great advantage, as only those infants affected with the less severe forms of the disease survive long enough for admission to a children's hospital. Nineteen of the 53 infants recovered, 24 died and 10 were stillborn. Necropsies were performed in all of the 34 fatal cases.

PRINCIPAL FEATURES OF ERYTHROBLASTOSIS

Familial incidence. There is a high familial incidence in erythroblastosis. In the present series, 16 of the 46 mothers had 2, and 4 had 3 affected infants, and, no doubt, the familial incidence will prove to be considerably higher when all these women have concluded their reproductive life. First infants seldom suffer from the disease, but, once it has appeared in a family, any subsequent infants are more likely than not to be affected. It remains to be shown, by careful observation for several weeks after birth, whether subsequent infants are ever entirely free from the disease. The available evidence suggests that heredity, also, may be an aetiological factor, but this aspect of the disease requires further study.

Clinical types. The relative frequency of the four clinical types of the disease is given in Table I. Nineteen unobserved cases from the affected families are included.

TABLE I.

The Type Distribution of Seventy-two Cases of Erythroblastosis Foetalis.

Type	No. of cases
Hepatic cirrhosis with maceration	9
Hydrops foetalis	8
Icterus gravis	47
Anaemia haemolytica	7

Anaemia haemolytica neonatorum is the least severe form of the disease. Anaemia is the predominant feature. There is not usually any jaundice but occasionally mild icterus, indistinguishable from the physiological type, occurs. The pallor, which may rapidly become severe, appears in the first 2 or 3 weeks of life. The liver and spleen are enlarged, although the latter may not be palpable. The blood shows the usual features of haemolytic anaemia, namely, hyperchromia, erythroblastaemia, and a variable degree of reticulocytosis depending on the re-activity of the erythropoietic tissues. Spontaneous recovery usually occurs but blood transfusion, which may have to be repeated, is sometimes necessary.

Icterus gravis is the commonest type of erythroblastosis. Two-thirds of the cases in the present series fall into this group. Jaundice, which is the predominant feature, distinguishes this type from anaemia haemolytica. It is either present at birth or appears within 24 hours, although, rarely, it may appear later. Early neonatal jaundice which rapidly becomes severe is almost a sure sign of icterus gravis. The golden yellow vernix found with congenital jaundice is often more noticeable than the jaundice itself. A severe degree of anaemia may already be present at birth and large numbers of erythroblasts of various types may be observed in the first few days of life. Spontaneous haemorrhage frequently occurs in the worst cases, the umbilicus and subcutaneous tissues being the commonest sites. It may occur any time within the first few weeks of life, thus distinguishing it from haemorrhagic disease of the newborn which is confined to the first few days. Degenerative changes in the basal nuclei of the brain are not uncommon and are revealed at autopsy by the bright yellow colour of the affected nuclei—hence the term kernicterus. Muscular rigidity and opisthotonus should arouse suspicion of kernicterus, but these clinical signs do not always occur. Death often occurs from toxaemia within a few days of birth. Infants surviving this critical period usually recover provided haemorrhage is controlled by the administration of vitamin K

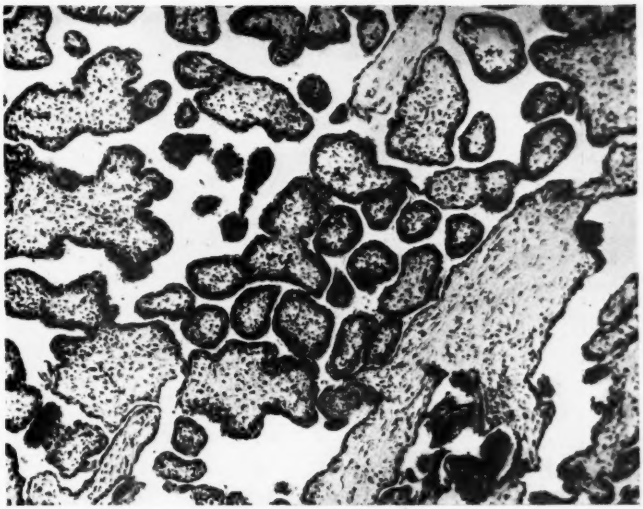

FIG. 1 (Case 3)

Erythroblastosis: 38 weeks' gestation. Placenta × 75. Abnormal epithelial persistence, which imparts an appearance of immaturity, is the salient feature.

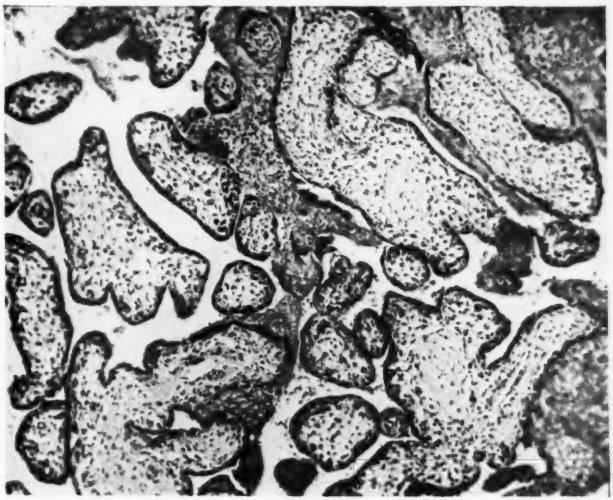

FIG. 2

Control placenta × 75.

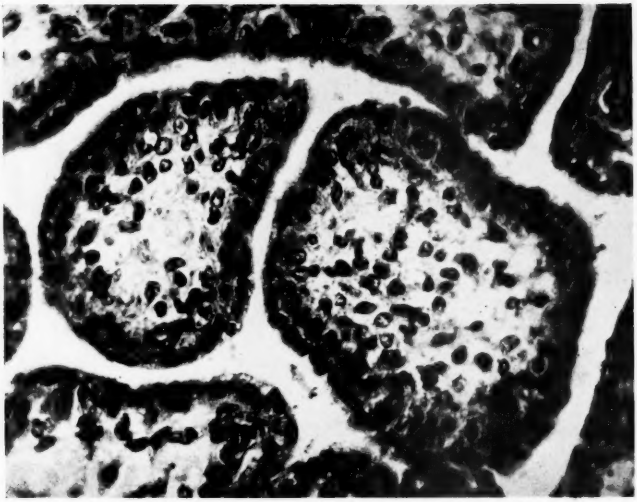

FIG. 3 (Case 3)

Erythroblastosis. Placenta × 350. Langhans' layer of cells, which should have disappeared by the 24th week of gestation, is almost complete in some of the villi. No blood vessels can be seen.

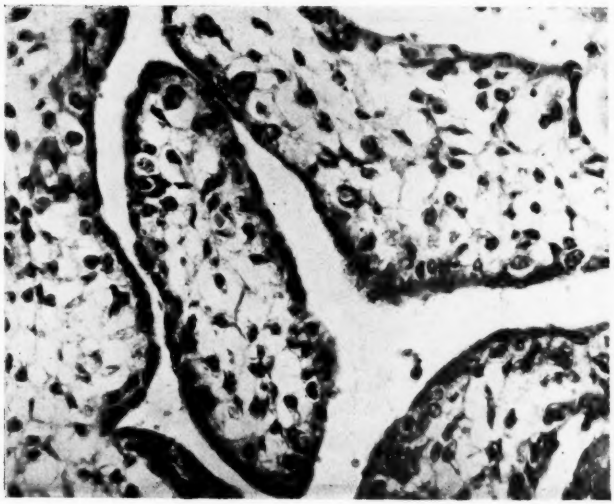

FIG. 4

Control placenta × 350.

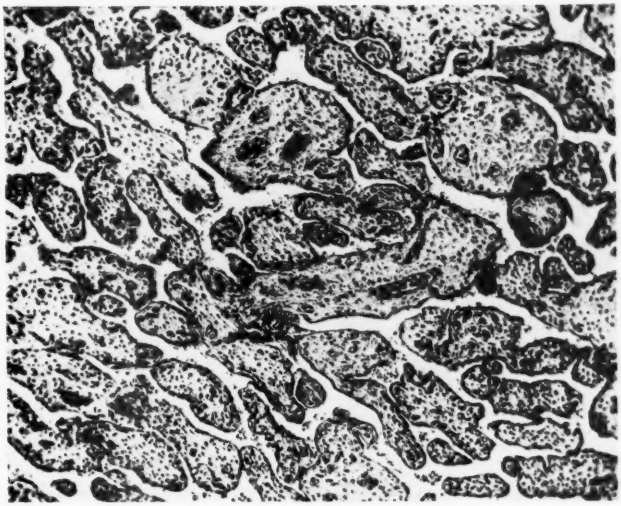

FIG 5.

Congenital syphilis: 24 weeks' gestation. Placenta × 75. Thickening of the villi and diminished vascularity with endarteritis are the principal features.

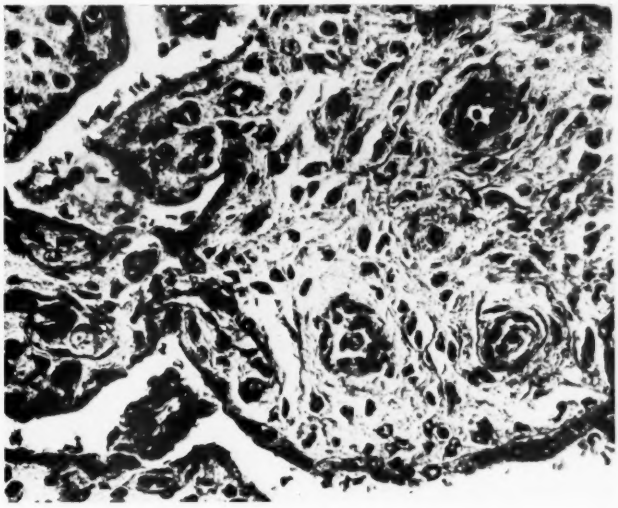

FIG. 6

Congenital syphilis. Placenta × 350. Obliterating endarteritis is well illustrated in this field. There is a considerable degree of fibrosis which is mostly peri-vascular. Note the absence of lymphocytic infiltration.

analogue and the haemoglobin is maintained at a safe level (40 per cent). Although spontaneous recovery often occurs in mild cases, blood transfusion is usually necessary in the more severe cases and may have to be repeated until the rate of erythropoiesis outpaces that of haemolysis.

Hydrops foetalis is a very grave form of erythroblastosis which is incompatible with independent life owing to the severe degree of hydrothorax preventing pulmonary aeration. Exceptionally, slight expansion of the lungs may occur when there is less hydrops but the period of survival rarely exceeds a few hours. Recovery in this form of the disease was first recorded recently in one of identical twins, the other suffering from anaemia haemolytica (Shapiro and Cohen[1]). Advanced foetal oedema can be diagnosed *in utero* by the radiological demonstration of a thickening and increased density of the soft parts. These features are most easily seen in the scalp where a definite corona surrounds the skull (Hellman and Irving[2]). The severe foetal oedema and greatly enlarged placenta are often responsible for a diagnosis of hydramnios, but this maternal complication occurs less frequently in hydrops foetalis than in the worse type of erythroblastosis with hepatic cirrhosis and intra-uterine death. Apart from the outstanding manifestation of universal oedema, the main features in this type of erythroblastosis are the same as in the less severe types of the disease except that there is little or no jaundice, a worse degree of anaemia and a greatly enlarged, pale pink placenta. The placenta assumes a pale grey colour on fixation.

Hepatic cirrhosis and intra-uterine death are the principal features in the fourth and worst type of erythroblastosis. Although this type seems to have escaped general recognition owing to the difficulties investigators have in obtaining macerated foetuses for examination, it seems probable that foetuses of this type with some oedema have often been classified as cases of hydrops foetalis. Hydramnios, during the last few weeks of pregnancy, is common in this form of erythroblastosis, and intra-uterine death of the foetus is followed within a week or two by the delivery of a severely macerated foetus and a greatly enlarged, pale pink placenta, as in hydrops foetalis. There is little or no oedema. The liver shows only slight enlargement, if any, and is usually greenish-brown in colour, while it is much less diffluent than the degree of maceration would lead one to expect and is definitely a little tough to cut. The spleen is greatly enlarged. It is so important to recognize this type of erythroblastosis and to

differentiate it from congenital syphilis, which it superficially resembles, that abstracts of the records of the 4 cases described in my original paper on this new type of erythroblastosis (Henderson[3]) are given below.

CASE 1. Baby O'M. Second pregnancy. Born July 9th, 1939.

Mother aged 35 years. Foetus of 7 pounds 1 ounce stillborn, at 40 weeks, and severely macerated. Mother well throughout pregnancy but had not felt life for a week before delivery when she had a heavy sickly feeling. Wassermann reaction, shortly after birth of this foetus, negative.

NECROPSY.

A well-developed male foetus showing advanced maceration. Pleural and peritoneal sacs contained blood-stained fluid, a normal feature in macerated foetûs.

Liver. About average size, olive green, and showed bile-staining throughout. It was firmer and less diffluent than might have been expected in view of the advanced maceration, and very slightly tough to cut.

Spleen. Greatly enlarged, measuring about 3 inches in diameter. It was soft and diffluent, and extensively macerated.

Placenta. Weight 1 pound 11 ounces (normal 1 pound 5 ounces). "Very unhealthy"; appearance not described.

Bones. Ribs and long bones did not show any macroscopic changes.

HISTOLOGY.

Haematoxylin and eosin sections of all the tissues examined showed advanced maceration.

Liver. All cell structure was lost but there was obviously a great increase of intercellular fibrous tissue reminiscent of congenital syphilis. This was confirmed with Azan's connective tissue stain.

Spleen. All cell structure was lost. Pathological changes could not be detected.

OTHER PREGNANCIES.

First pregnancy. Infant of 5 pounds 2 ounces born alive, at 38 weeks, in 1937, apparently healthy and survived.

Third pregnancy. Infant of 5 pounds 10 ounces born alive, at 39 weeks, in 1941, with severe jaundice. Placenta weighed 1 pound 3 ounces but appearance not mentioned. Liver and spleen enlarged. Numerous subcutaneous ecchymoses. Three hours after birth, prothrombin index 34 per cent and haemoglobin 43 per cent (Sahli). Reticulocytes greatly increased. Death occurred 37 hours after birth. The usual features of icterus gravis were seen at necropsy. Icteric index of post-mortem blood serum was 254. Microscopic examination of the liver showed the usual features of erythroblastosis, most of the erythropoietic foci were chiefly composed of large primitive erythroblasts. There was also some increase in the intercellular reticulum throughout the liver lobules, so that the cell columns were more separated from each other than usual. The portal tracts contained about the normal amount of fibrous tissue. There was no fibrosis in the spleen.

CASE 2. Baby S. Third pregnancy. Born September 14th, 1941.

Mother aged 35 years. Foetus of 5 pounds 10 ounces, stillborn, at 36 weeks, and severely macerated. Mother had hydramnios for about the last 6 weeks of the pregnancy and had not felt life for the last 2 weeks. Wassermann reaction negative.

NECROPSY.

A small male foetus. Abdomen distended but not tense. Some oedema of face and head. Advanced maceration.

Thorax. Serous sacs contained a quantity of blood-stained fluid not notably in excess of that invariably found in macerated foetûs. Heart looked a little above the appropriate size, it was dilated and flaccid owing to maceration. *Abdomen*. Peritoneal sac contained a large quantity of blood-stained fluid definitely in excess of the amount usually found in a macerated foetus.

Liver. Moderately enlarged, yellowish-brown, fairly soft to the touch but definitely a little tough to cut. Its surface was perfectly smooth. It was much less diffluent than might have been expected from the stage of maceration that had been reached, and had kept its consistency much better than any of the other organs. Its colour was quite unlike the usual dull pink of ordinary macerated livers. The appearance suggested that there might be some fine diffuse fibrosis.

Spleen. Much enlarged, being nearly 3 inches in diameter. It had undergone autolysis and was very soft and diffluent.

Placenta. Weight, 2 pounds 9 ounces (normal, 1 pound 5 ounces). It had a pale pink colour; other observations were not recorded.

HISTOLOGY.

Liver. Haematoxylin and eosin sections showed advanced maceration; no cell structure or nuclear staining remained. A diffuse, fairly uniform, fine intercellular fibrosis was visible and confirmed by application of Masson's connective tissue stain. It was a little denser in some parts than in others, but these bore no relation to zones of the hepatic lobule.

Spleen. Apart from autolytic changes, did not show anything of interest. Sections of all tissues stained by Dobell's method did not reveal any spirochaetes.

PREVIOUS PREGNANCIES.

First pregnancy. Infant of 8 pounds 8 ounces born alive, at 40 weeks, in 1933, apparently healthy and survived.

Second pregnancy. Infant of 8 pounds 3 ounces born alive, at 40 weeks, in 1938, with severe jaundice. Placenta weighed 1 pound 10 ounces; appearance not mentioned. Liver and spleen enlarged. Haemoglobin 84 per cent (Sahli), reticulocytes 35 per cent and many nucleated erythrocytes. Death occurred 38 hours after birth. Necropsy showed the usual features of icterus gravis and the occasional one of kernicterus. Microscopic examination of the liver showed very excessive erythropoiesis, many of the erythroblasts being of a primitive type. There was not any fibrosis in either liver or spleen.

CASE 3. Baby T. Seventh pregnancy. Born September 15, 1941.

Mother aged 28 years. Foetus of 6 pounds 2 ounces, stillborn, at 38 weeks, and severely macerated. Mother felt very well throughout pregnancy but had not felt life for 10 days before delivery. Some hydramnios was observed on admission 4 days before delivery. Wassermann and Kahn reactions were negative after provocative injection during this pregnancy. In spite of this a course of anti-syphilitic treatment was contemplated after the birth of the second macerated foetus.

NECROPSY.

A small male infant showing advanced maceration. Serous sacs contained a quantity of blood-stained fluid, a common feature in macerated foetuses.

Liver. A little enlarged. Light brown in colour with a greenish-yellow tinge suggesting jaundice. Not hard but seemed slightly tough to cut. Autolysis associated with maceration had not caused it to disintegrate as much as might have been expected and it was not diffluent. Quite smooth on outer surface.

Spleen. Enlarged to about 2 inches in length. Soft, but not diffluent.

Placenta. Weight 2 pounds 15 ounces (normal 1 pound 5 ounces), it was very thick and had a pale pink colour.

HISTOLOGY.

Liver. Cell structure destroyed by maceration, nuclear staining absent. A diffuse, fine, intercellular fibrosis was shown to be fairly uniform and abundant with Masson's stain. Haemopoietic foci not recognizable. Sections of liver and spleen stained by Dobell's method did not show any spirochaetes.

Spleen. Cell types not recognizable although a certain amount of nuclear staining retained. No fibrosis.

Placenta. Figs. 1 to 4. Villi thickened, with relatively narrow intervillous spaces. The most striking feature was an abnormal persistence of Langhans' layer of cells in some situations. The villous capillaries were small and inconspicuous. The syncytial cells were somewhat large and numerous. The stroma was oedematous and an increased proportion of the stroma cells showed enlarged, palely-staining nuclei. Erythropoietic foci were not observed, but numerous erythroblasts were seen in the vessels.

Suprarenals. A few foci of erythroblasts.

PREVIOUS PREGNANCIES.

First pregnancy. Infant of 8 pounds, born alive, at 40 weeks, in 1933, apparently healthy and survived.

Second pregnancy. Infant of 9 pounds 8 ounces, born alive, at 40 weeks, in 1935, apparently healthy and survived.

Third pregnancy. Infant of 6 pounds 8 ounces, born alive, at 40 weeks, in 1936, became " extremely bloodless " and died aged 3 weeks. This infant probably died from erythroblastosis of the anaemia haemolytica type.

Fourth pregnancy. Infant of 6 pounds 8 ounces, born alive, at 40 weeks, in 1938, and died aged 2 days. No evidence obtainable but may well have died from erythroblastosis.

Fifth pregnancy. Foetus of ? weight, stillborn, at 32 weeks, in 1939, when

mother suffered an antepartum haemorrhage. Foetus appeared normal, but may have been affected with erythroblastosis.

Sixth pregnancy. Foetus of ? weight, stillborn, at 40 weeks, in 1940, in a macerated condition. Attending doctor felt sure it was syphilitic owing to its appearance and that of the placenta. This can certainly be regarded as a case of erythroblastosis in view of the necropsy findings in the foetus and placenta of the 7th pregnancy.

CASE 4. Baby Y. Fifth pregnancy. Born December 12th, 1941.

Mother aged 37 years. Foetus of 9 pounds 5 ounces, stillborn, at 38 weeks, and severely macerated. Mother felt very well until 2 weeks before delivery, when she developed headaches, vomiting, oedema of the ankles and a trace of albumin in the urine. These symptoms became worse and a severe degree of hydramnios developed in the last fortnight of pregnancy. Life was not felt for 10 days before delivery. The day after admission to hospital the membranes, which protruded through a three-fingers dilated os, were ruptured and 7 pints of brown coloured liquor amnii escaped. Another 2 to 3 pints of fluid drained away after the birth of the foetus 2 hours later. Wassermann reaction negative.

NECROPSY.

A large female foetus. A little oedema of the face and upper part of the thorax, but none in the limbs. Abdomen enlarged but abdominal wall quite lax. Advanced maceration. *Head.* Nothing pathological recognized. *Thorax.* Pleural sacs contained a considerable quantity of blood-stained fluid not notably in excess of that commonly found in macerated foetuses. Pericardial sac contained only a small quantity of blood-stained fluid. Lungs showed nothing noteworthy. Heart seemed a little enlarged but this may have been the result of relaxation of the wall owing to maceration. *Abdomen.* Peritoneal sac contained only a small quantity of blood-stained fluid. Alimentary tract showed nothing of interest.

Liver. About average size, weighed 180 grams. Rather firmer than expected in view of the degree of maceration present, slightly greenish-brown and definitely, though slightly, tough to cut. There was no visible fibrosis and the outer surface was perfectly smooth.

Spleen. Immensely enlarged, weighed 70 grams and measured fully 5 inches in length. Its lower pole lay to the right of the middle line and much of the abdominal enlargement was due to its great size. It was soft, lightish red, and showed advanced maceration.

Placenta. Weight 3 pounds 15½ ounces (normal 1 pound 5 ounces). Diameter 10 inches. Thickness 1¼ inches. Pale pink colour.

Other organs showed nothing of interest.

HISTOLOGY.

Liver. Autolysis advanced with loss of all cell structure and nuclear staining. There was a diffuse fine fibrosis which was present everywhere, but varied a little in degree from place to place, although it had no zonal distribution. It was readily perceptible in sections stained with haematoxylin

and eosin, but was shown to much greater advantage by Masson's connective tissue stain. Spirochaetes not seen with Dobell's stain.

Spleen. Very little nuclear structure remained. No fibrosis.

Blood. A film of heart blood had resisted autolysis better than might have been expected. It showed a very great increase in the number of nucleated red cells, including many very primitive forms.

Placenta. Histological characters similar to those seen in Case 3. Villi enlarged, with relatively narrow intervillous spaces. The villous capillaries were small and inconspicuous. The characteristic persistence of Langhans' cells could be seen here and there. The syncytial cells were somewhat large and numerous. The stroma had an oedematous appearance in some places and an increased proportion of the stromal cells showed enlarged, palely-staining nuclei. Erythropoietic foci were not observed, but numerous erythroblasts were seen in the vessels.

PREVIOUS PREGNANCIES.

First pregnancy. Miscarriage.

Second pregnancy. Infant of 7 pounds born alive, at 40 weeks, in 1933. Apparently healthy in infancy. Developed poliomyelitis later.

Third pregnancy. Infant of ? weight, stillborn, at 40 weeks, in 1938. Anencephaly. No autopsy.

Fourth pregnancy. Infant of 3 pounds 13 ounces born alive, at 28 weeks, in 1940, following an ante-partum haemorrhage. The placenta weighed 1 pound 4 ounces, but further details are not available. The infant died aged 11 hours. Nothing of much interest was found at autopsy. The cerebral hemispheres were excessively congested and a considerable degree of haemorrhage was seen in the posterior part of the falx cerebri. The lungs were almost completely atelectatic and sank in water. Histological examination was not made.

DIFFERENTIATION OF ERYTHROBLASTOSIS FROM CONGENITAL SYPHILIS

The two most severe forms of erythroblastosis, hydrops foetalis and the type with hepatic cirrhosis in cases of intra-uterine death, are usually mistaken for congenital syphilis on account of the large, pale coloured placenta which occurs in both of these types of the disease. Much emphasis has been placed on this feature and the occurrence of a succession of stillborn foetuses as characteristic signs of congenital syphilis, but it is not generally known that these signs also occur in the more severe forms of erythroblastosis. These and other points of resemblance between the two diseases such as extramedullary haemopoiesis and hepatic cirrhosis, account for the frequency with which erythroblastosis is mistaken for congenital syphilis, the better known disease. They render careful differentiation imperative, but

uncertainty will seldom arise if all doubtful cases are carefully investigated along the following lines.

Familial incidence. The occurrence of a proved case of either disease in a previous sibling almost clinches the diagnosis, but such valuable evidence is seldom available. It is generally believed that the course of a succession of syphilitic pregnancies tends to pass from abortion through successively longer pregnancies to the birth of macerated or stillborn foetuses, then premature living syphilitic, and finally of full-time living syphilitic or apparently healthy offspring. Although this sequence is seldom realized, a tendency for the disease to become progressively less severe can often be seen. In erythroblastosis, the trend is in the opposite direction. First pregnancies are seldom abnormal in affected families and several healthy infants may be born before the disease appears. It often assumes a graver form in successive pregnancies until either hydrops foetalis with stillbirth or hepatic cirrhosis with intra-uterine death may be expected. Nevertheless, cases of intra-uterine death are followed, not infrequently, by the birth of infants with milder forms of the disease who may survive.

Maturity. The frequency and degree of prematurity are much higher in syphilitic infants than in those affected with the hydropic and macerated types of erythroblastosis. Very premature infants with an enlarged pale placenta are much more likely to be suffering from syphilis than erythroblastosis, unless severly hydropic. There does not appear to be any tendency to prematurity in either the anaemia haemolytica or icterus gravis types of erythroblastosis. My experience does not conform with that of some authors who have observed an increased incidence of abortion in families affected with erythroblastosis. This is much commoner in syphilitic families.

The placenta. There is a general impression that careful examination of the placenta is seldom worth while and, consequently, many abnormal placentas which should be retained for examination are destroyed and valuable evidence is lost. For instance, it is not only of great value in the differential diagnosis of the two diseases under consideration, but it sometimes supplies the strongest evidence of congenital syphilis in a suspected case when the mother's serological tests are negative. The placenta does not show any macroscopic abnormality in the anaemia haemolytica and icterus gravis types of erythroblastosis, but in hydrops foetalis and the type with hepatic cirrhosis and intra-uterine death, it has a pale pink colour, its thickness is greatly

increased and it may weigh several times as much as the normal placenta. In a recent case of the hydropic type, the 29-weeks foetus weighed 4 pounds 14 ounces and the placenta weighed 3 pounds 15½ ounces. In syphilis, also, the placenta has a pale pink colour and an increased thickness and weight, but infarction, which is not a feature in erythroblastosis, is usually found in addition. Multiple small infarcts, which may be missed on superficial examination are commoner than large ones in the placenta of the liveborn syphilitic infant, but large infarcts often occur when the syphilitic process is more advanced as in the case of a macerated foetus.

The histological features of the placenta in the two diseases bear a superficial resemblance which might deceive the inexperienced, for the villi show enlargement and diminshed vascularity in both conditions. One cannot look far in a syphilitic placenta, however, without encountering areas of infarction. In cases of erythroblastosis with enlargement and pallor of that organ, a persistence of Langhans' layer of cells, which can be seen here and there, is the most characteristic histological feature. They cannot invariably be seen in these worse forms of the disease, however, and rarely in icterus gravis and anaemia haemolytica. These cells normally disappear by the 24th week of pregnancy and their persistence to term is not known to occur in any other disease. They can easily be distinguished from the overlaying syncytial cells by their larger and paler nuclei and cuboidal or columnar shape (Fig. 3). The syncytial cells tend to be larger and more numerous than in the average mature placenta. Other abnormal features are the small size and inconspicuousness of the villous capillaries, a variable degree of oedema in the stroma and a great increase in the nucleated red cells in the vessels. The increased proportion of large palely staining cells in the stroma imparts an appearance of increased cellularity, but a similar appearance is sometimes seen in normal placentas, in which the stromal cells show considerable variation in character. Erythropoietic foci are said sometimes to occur in the villi, but I have not yet observed any sign of blood formation in the placenta. The apparent immaturity of the placenta in erythroblastosis was first mentioned in the literature by Hertig (Diamond, Blackfan and Baty[4]). More recently, Hellman and Hertig,[5] in a contribution on pathological changes in the placenta in erythroblastosis, concluded that in the hydropic type the pathological changes in the epithelium, stroma and vessels constitute a syndrome which is pathognomonic of the disease

and that similar but less advanced changes occur in icterus gravis. They also point out that somewhat similar features occur in immature placentas and in the epithelium from hydatidiform moles and cases of chorionepithelioma. These authors did not refer to the placenta in the anaemia haemolytica type of erythroblastosis nor did they seem to recognize the gravest form of the disease with hepatic cirrhosis and intra-uterine death in which the placental changes are similar to those seen in hydrops foetalis.

In the syphilitic placenta (Figs. 5 and 6) there is abnormal epithelium persistence and the villous capillaries are much more conspicuous than in erythroblastosis owing to their thickened walls, various degrees of endarteritis up to complete occlusion being a prominent feature. Fibrosis in the stroma of the villi, which is mostly concentrated around the affected vessels, is also a prominent feature. There is an increased proportion of large palely staining cells in the stroma, as in erythroblastosis. The widespread belief that lymphocytic infiltration is one of the essential criteria of the syphilitic placenta is unfortunate, for there may not be any "small round-celled infiltration" in the earlier stages of the disease process, as in a recent case of congenital syphilis in a live-born infant, in which, on naked-eye examination, the placenta showed typical syphilitic features. The spirochaeta pallida was demonstrated in the liver in this case from which Figs. 5 and 6, showing the abnormal placenta, were taken.

Extramedullary erythropoiesis. Congenital syphilis and erythroblastosis resemble each other most closely in their haematological aspects. There is an erythropoietic response to toxic haemolysis in both conditions. Extramedullary erythropoiesis with hepatosplenomegaly occurs in both diseases and the blood shows a hyperchromic anaemia with erythroblastaemia and reticulocytosis. These features, along with jaundice, which may occur in the syphilitic infant, may cause a newborn infant with congenital syphilis to resemble the icterus gravis type of erythroblastosis very closely. The liver is heavily infiltrated with erythropoietic cells in both diseases, but in erythroblastosis the distribution is usually focal and there is a considerable proportion of more immature lightly staining erythroblasts, whereas, in congenital syphilis, the distribution is diffuse and most of the immature cells have reached the normoblast stage. Small, sparsely scattered foci of erythropoiesis are often seen in the liver of the normal newborn infant; this feature is commoner in the case of premature infants but even in them it is abnormal to see more than a few small foci in a low power field. Excessive

erythropoiesis is also seen in the spleen in both diseases but its degree is much more difficult to assess in that organ than in the liver. Blood formation in other organs, such as the kidney, may also be found in both diseases.

Hepatic and splenic cirrhosis. The diffuse intercellular cirrhosis of the liver which is found in congenital syphilis and in the severest type of erythroblastosis (vide cases 1-4) can often be distinguished by the occurrence of miliary gummata in the former disease. Occasionally, an early diffuse cirrhosis is found in hydrops foetalis and icterus gravis, but central and periportal cirrhosis is much commoner in these types of erythroblastosis. In the spleen a considerable degree of diffuse fibrosis is a constant feature in syphilis, whereas one only occasionally sees slight fibrosis in erythroblastosis.

Osteochondritis. This was regarded as a very frequent manifestation of congenital syphilis by the older writers. It would appear to be a feature in over 50 per cent of cases. It is usually present at birth, but may not appear for several months. Chondro-epiphysitis is the commonest lesion but periostitis frequently occurs. Osseous manifestations are absent in erythroblastosis, although an osseous sequela has been described. The demonstration at autopsy of a thick, irregular and yellowish epiphyseal line in the long bones is a very valuable sign of congenital syphilis.

Specific serological reactions. The reactions in the specific serological tests for syphilis in the mother, though not infallible, are of value in differentiating the two diseases in doubtful cases. They are of much less value in the newborn infant in whom the reactions are untrustworthy for at least 10 days after birth.

Spirochaeta pallida. Finally, it is clear that the demonstration of the spirochaeta pallida in the tissues of the foetus, cord or placenta would dispel any lingering doubt, but it must always be remembered that the organism is very much more difficult to demonstrate in fresh than in macerated tissues. The spirochaeta pallida can more often be found in scrapings of the tunica intima of the umbilical vein than in the placenta where it is usually difficult to demonstrate.

Summary

The principal features of the common foetal and neonatal disease known as erythroblastosis foetalis have been summarized.

There are four clinical types of the disease:

1. Anaemia haemolytica, the mildest form, which often

escapes notice unless severe. Spontaneous recovery usually occurs.

2. Icterus gravis in which severe jaundice is seen either at birth or within a few hours thereof. Spontaneous recovery may occur but blood transfusion is often necessary. The mortality is about 50 per cent.

3. Hydrops foetalis in which universal oedema precludes the establishment of independent life and stillbirth occurs.

4. Hepatic degeneration and cirrhosis with intra-uterine death and severe maceration of the foetus.

Four cases of the most severe type of erythroblastosis with intra-uterine death of the foetus have been recorded in detail, as this type of the disease is not well known.

It is usually mistaken for congenital syphilis on account of the intra-uterine foetal death, which may have occurred in previous siblings also, the diffuse hepatic cirrhosis, and the greatly enlarged pale pink placenta which most people have been taught to regard as syphilitic.

The differential diagnosis of erythroblastosis and congenital syphilis has been discussed,

The histological features of the placenta in the two diseases have been contrasted and found to show distinctive features.

Erythroblastosis foetalis is the only disease in which persistence to term of Langhans' layer of cells in the chorionic villi is known to occur.

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Contribution to the Aetiology of the Toxaemic Syndrome of Pregnancy

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IT is generally acknowledged that, under pathological conditions, a diversion of venous blood may occur from the portal system to the caval systems. Perhaps the most universally recognized example of this is the development of the "caput Medusae" around the umbilicus in cases of hepatic cirrhosis. This represents an anastomosis by which blood in the portal vein, unable to pass the liver, finds its way to the heart through one of the many communicating channels which exist between portal and systemic circulation: namely via veins in the round ligament of the liver to the abdominal wall, and thence to the superior and inferior caval systems through the epigastric veins. Another very important example, which has been fully discussed by the present author elsewhere,[1] occurs in cases of haemorrhoids. In this condition blood may flow at times from the portal system, via the haemorrhoidal plexuses, to the caval system, and when an individual suffering from haemorrhoids suddenly loses a pint or more of blood at stool, it is *portal blood* which is lost. If proctoscopy is performed on the same patient shortly afterwards the bleeding point may be easily visible, but the escape of blood will now be a mere trickle, for the patient is lying down and relaxed, and the hindrance (straining at stool) to the normal return of the portal blood is no longer operative.

In the author's experience, patients with a varicocele have always large haemorrhoidal varices, and it seems likely that in these cases an enlargement has occurred of normal communications between the pampiniform plexus and the pudendal plexus[2] in the pelvis.

The conception of the tributaries of the internal iliac vein as forming a plexus is not common among English writers; but its constitution and extent may be understood from the following description written by M. E. Paul, in his translation of Toldt's Atlas of Anatomy:[2] "Vesical, Prostatic and Pudendal Venous

Plexuses. The vesical venous plexus consists of veins which ramify over the whole surface of the bladder external to its muscular coat; they are larger and more numerous round the base of the organ, receiving here veins from the ureters, the vasa deferentia, and the vesiculae seminales, and communicating freely with the prostatic and haemorrhoidal plexus. The prostatic venous plexus, which is formed largely by the breaking up of the dorsal vein of the penis, ramifies between the two layers of the pelvi-prostatic capsule. Its connexion with the vesical plexus is so intimate that Macalister describes the two under the joint name as the 'Prostatico-vesical Plexus.' In the female, the place of the prostatic plexus is taken by a plexus surrounding the upper part of the urethra and receiving the dorsal vein of the clitoris. The vaginal plexus also communicates freely with the vesical plexus in front and the haemorrhoidal plexus behind. Thus, the pudendal plexus of Toldt (the term is little used in England) is made up in the male of veins regarded by English anatomists as belonging to the prostatic plexus, and in the female of veins belonging to the peri-urethral, vesical, vaginal and uterine plexuses."

These are only a few of the many communications which have been described between the two vascular systems, but Table I shows a more complete list taken from Thomas.[3] The significance of the existence of all these anastomostic channels is discussed later in this paper.

The main purpose of the present paper is to consider whether an exactly similar but physiological diversion of the blood-stream does not occur during normal pregnancy. Many multiparae are able to diagnose their own successive pregnancies as early as the 4th week by the development of haemorrhoids, pruritus, or varicosities of the leg veins. These signs disappear if abortion or death of the foetus occurs. An adequate explanation of these facts cannot be given on a basis of pressure by the growing uterus on its venous return; yet it is obvious that even at that early stage of the pregnancy some profound change is occurring in the venous drainage of the genitalia. These changes are not seen, it should be noted, when the uterus is much more grossly enlarged as a result of myomata or other tumours or when the lower abdomen is filled by a large ovarian cyst.

A much more likely explanation suggests itself if these changes are considered alongside the development of the foetal circulation. During the first 4 weeks the foetus is nourished from the yolk sac (vitelline circulation). From the store in the yolk sac ready

prepared substances are conveyed to the growing foetus, and with very little metabolic change are built up into its body tissues. But as the rapid growth of the ovum proceeds, a more elaborate system is needed, and the chorionic villi begin to form, so that by about the 12th week the new placental circulation is complete. The placenta is as one lung, liver, and spleen to the foetus. Through it " the nutrient amino-acids pass to, and the catabolites urea and uric acid pass from, the foetus through the placenta by diffusion." (Givens and Howe.[4]) The foetal growth is very rapid, and as it becomes larger, more and more products of its metabolism pass from it through the placenta. This outflow of metabolites will be greatest in the last third of pregnancy. That substances can pass from the foetus to the mother was suggested by Harvey and McGillivray,[5] and proved by Savory in 1858.[6]

What is the nature of these metabolic breakdown products, and how does the mother deal with them? They may be presumed to be toxic, or the foetus would not need to excrete them. How does the mother detoxicate them? Now the organ primarily concerned in making absorbed substances safe for the bloodstream is the liver. In this great chemical factory all the foreign substances taken into the body from the bowel are dealt with; they are rendered suitable for passage into the general circulation and use by the rest of the body. Is it likely that the great access of excreted matter coming from the foetus would be allowed to pass straight into the mother's general circulation? In the author's view it is much more probable that during pregnancy the venous drainage of the placenta and, therefore, of the uterus, is diverted to the portal system and the liver, and the development of this diversion, with the enormous enlargement of the pudendal plexus which it necessitates, causes the blueing of the genitalia already mentioned. The uterine veins do not have any valves. The tributaries of the internal iliac veins anastomose with the vesical plexus and the haemorrhoidal plexus, and thus through the inferior mesenteric vein with the portal vein.

In further support of the hypothesis may be quoted a statement from Boyd.[7] Speaking of the liver in eclampsia, he says: " The necrosis is peripheral in type, being most marked around the portal vein in contradiction to the central necrosis of acute yellow atrophy and the ordinary necrosis. Syncitial masses from the placenta may be presented in this area."

By what other route could these cell-masses have reached the liver save by the portal vein? The evidence is that the uterus, at any rate in eclampsia, is draining into the portal system.

If it be agreed that this change takes place in every pregnancy, we are enabled to formulate an entirely new theory of the toxaemias. Previously it has been supposed that the mother is poisoned by toxins, admittedly foetal in origin, but coming in excessively large amounts, or in abnormal forms. But the minor forms of toxaemia are so common, albuminuria in one out of 3 pregnancies,[8] that it becomes necessary to assume that a large proportion of foetûs is abnormal. It is much more reasonable to suppose that the mother is at fault: and it is now easy to see how this may be. Either the normal diversion of placental blood to the liver is delayed or imperfect, or there is some liver defect which impairs its detoxicating function. In either case substances which otherwise would never reach the general circulation are allowed to enter the systemic blood-stream, and so reach all parts of the body, producing damage in brain, kidney and elsewhere. It has long been known that the liver enlarges during pregnancy, and that its integrity is tested by the increased burdens placed upon it at this time. (De Lee.[9]) But no one has asked the question why the liver should be specially affected, if toxic products reach it, as is generally supposed, only indirectly after passing through the general circulation.

It will be useful at this point to consider some of the many changes which occur in the circulation of the foetus itself during gestation. After the change-over from the vitelline to the placental circulations, numerous other modifications occur in the foetal vascular system—in the arteries of the bronchial arches, for example, and later at the time of birth, in the foramen ovale of the heart, the Eustachian valve, the ductus arteriosus of Botallus, the hypogastric arteries, and, in the portal system, the ductus venosus of Arantius. We may in fact observe a continual adjustment, involving the development of temporary vessels and systems of by-passes, obliteration of others, and diversions of the blood-stream, until the final permanent stage is reached. Of particular interest in relation to the subject of this paper is the ductus venosus. Although the umbilical vein is a tributary of the portal vein, there is no need for the blood it brings to be carried to the liver for alteration or detoxication, so nature provides in the ductus venosus a by-pass conveying the blood direct into the inferior vena cava. The liver is superfluous in the alimentary sense, for the nutrient substances from the placenta are already prepared, and there is no absorption from the bowel to be dealt with. Within a few weeks of birth the ductus venosus becomes transformed into a fibrous cord (ligamentum venosum);

for the blood must now be made to pass through the liver in order that its contents of partly modified food may be dealt with there. We may assume that if the liver failed to take over this function, or was slow to do so, poisoning of the child would result; indeed such an event would furnish a likely explanation of the phenomenon of icterus neonatorum. Premature closure of the duct, on the other hand, might find the liver unprepared to take over this function, with similar results.

Morning sickness. This is one of the first signs of pregnancy, sometimes commencing in the 4th week, and persisting until the 12th week. Its appearance thus coincides with the blueing of the vulva, and therefore, according to the conception we are discussing, with the transfer of the uterine blood to the portal system. It may be explained as due to a mild toxaemia inevitable while the circulatory changes are as yet incomplete, and accentuated if they are delayed. What method is adopted by the body for changing over the uterine drainage to the portal system is still a matter for conjecture—whether by thrombosis and obliteration of existing vessels, or by collapse and spasm of one set and dilatation of another, or by means of by-passes and alternative routes. It is probable that, whereas in a normal pregnancy the symptoms pass off at about the 12th week because the cavo-portal connexions are in full working order, in other cases the vomiting becomes worse and the condition passes into one of true clinical toxaemia (hyperemesis gravidarum) because the change-over is delayed. As would be expected, morning sickness is commonest in primigravidae, and if it occurs in later pregnancies it is usually less severe. This is presumably because the diversion of the circulation takes less time to establish and is brought about more smoothly each time the process is repeated. Morning sickness ceases if the foetus dies, or if abortion occurs, because the source of the toxins is no longer active.

Hyperemesis gravidarum. The healthy woman meets all demands of the development of the new circulation without difficulty, and her liver is able to detoxicate the new toxins brought to it, without any sign of insufficiency; but a woman with a liver previously damaged by disease may fail. The conception of low-reserve-power liver is not a new one. It is well known that previous liver diseases predispose to hyperemesis and eclampsia. It is probable that diseases as diphtheria, scarlet fever, chorea, or erysipelas, which damage the kidney, may damage the liver also. But as it is much harder to examine the liver function and reserve than that of the kidney, the hepatic insuffi-

ciency may remain latent and unsuspected until brought to light by the strain of pregnancy. We must now consider the question of the effect of an inefficiently working liver on the portal blood-pressure. In the French literature, the term hypertension portale is well known. Under the "Syndrome de l'hypertension portale" the following symptoms are grouped: "L'opsurie (diminished and delayed secretion of urine), l'ascite, la splenomégale, les haemorrhoides, les haemorrhages gastro-intestinales, développement anormale de la circulation souscutanée abdominelle."[10] The portal blood-pressure depends upon the vital activity of the mucosa of the bowel, the cells of which are thrusting fluid into the system, and that of the liver cells, which are passing the fluid on to the general circulation or the bile. It, therefore, follows that any intoxication of these liver cells will result in portal hypertension, with a consequent diversion of the contained blood into the caval systems through the anastomotic channels. The impressive list of these channels shown in Table I suggests that their presence is no accident, but that they must serve some useful purpose. It is at least likely that they act as a safety-valve for the portal system—as indeed we know they do in cirrhosis of the liver. Now where the leakage of portal blood is considerable in amount, as in the terminal stages of cirrhosis, the condition of hepatic coma develops; and consideration of this clinical picture of convulsions and unconsciousness will show how closely the condition resembles eclampsia. It is worth recalling that in times past physicians referred to the portal vein as "porta malorum."

In birds the portal vein has a large branch which enters the kidney, its capillaries surrounding the tubules. (Hence it would seem that their kidneys are adapted to the detoxication of substances in the portal blood.) In man this vein is said to be represented by the capsular veins of Retzius. These drain into the right renal vein, and their existence was known to Claude Bernard[11] and to Villaret. Henschen[12] found these collaterals to be dilated in cases of hepatic cirrhosis. (Another porto-renal anastomosis already mentioned is via the pampiniform plexus.) During pregnancy, and especially in hyperemesis gravidarum, the hypertension in the portal system may lead to a diversion of both maternal and foetal toxins direct into the kidney. It is a possibility that this occurs also in Bright's disease. The conception affords a ready explanation of the fact that decapsulation of the kidney, thus cutting off its connexion with the portal system, may lead to relief of eclampsia.

It is customary to describe two types of hyperemesis, the functional or neurotic, and the toxic. There is very little evidence that the two are in reality of different nature. A possible explanation of the differences is that the so-called neurotic type may be due to a disturbance or delay in the development of the collaterals of the porto-caval anastomoses; whereas the toxic type may be the result of the low-reserve-power liver, or to an acute disease of the liver cells.

Some of the symptoms associated with toxaemia in pregnancy may now be considered. Anal and vulval pruritus, according to De Lee, is "an affection perhaps toxaemic, usually localized on the vulva, sometimes general, which begins in the middle or end of pregnancy and may reach such an intensity as to demand the emptying of the uterus." The author has elsewhere[1] explained how in his opinion pruritus of the anus, vulva and groin may be caused by the escape of portal blood through the haemorrhoidal plexus into the systemic circulation, so that the pruritus of pregnancy would have an exactly similar explanation. Like the pruritus in rectal varicose disease, that of pregnancy is worse at night; it disappears with delivery, but reappears in subsequent pregnancies.

The high blood-pressure of the toxaemias may be provoked by the rising pressure and stasis in the portal system. Peller[13] has made an exhaustive study of the effects of experimental venous stasis on the circulatory system itself. He was able to show that venous stasis produced an increase of pressure on, and alteration of the tone of the smooth muscle of the arteries. The effect of the stasis in a given area is not confined to that area, but is produced also on the smooth muscle of vessels at a distance. The muscle reacts first to venous congestion by increase of tone, by cramp or spasm, such as is found with varicose veins. Thus in pregnancy an increased arterial tone might be due to a portal hypertension. Or it might be a direct effect on the intima of the vessels by toxins which have succeeded in reaching the general circulation. It might even be due to the increase in the amount of fluid in the caval system, caused by the diversion into it of blood from the portal system.

Albuminuria has been explained as due to lordosis, to bacterial infection, or to abnormal permeability of the capillaries. But the albuminuria could also be explained as the result of intoxication of the kidneys by poisonous waste products. In the same way the pyelitis and cystitis so common in pregnancy might be accounted for, the infection being merely secondary to

the intoxication. *Glycosuria* may conceivably be due to chronic induration of the pancreas produced by the portal stasis. That the vomitus in hyperemesis finally becomes bloody may have the same explanation as in cirrhosis, when it is a well-known symptom. Here it is due to obstruction in the portal circulation, so that the pathology in hyperemesis may well be identical. The bleeding is comparable with that from haemorrhoids or oesophageal varices. Other manifestations of pre-eclampsia, such as jaundice, cerebral symptoms, acidosis, tenderness of the liver, gingivitis, vomiting, and the haemorrhagic diathesis, are equally easy to explain.

Eclampsia. This condition is only a higher degree of the same toxaemias already described. There is no difference in quality between hyperemesis and eclampsia; the only clinical distinction is the acuteness of the latter disease. If death does not follow eclampsia, the result is in every case a more or less damaged liver, and the pathological-anatomical findings correspond with those of a portal cirrhosis. The acute yellow atrophy is not a clinical entity, but an end result of any acute liver disease—formerly grouped as icterus gravis. It is impossible to differentiate histologically the findings in the liver from those of acute chloroform, phosphorus or mushroom poisoning.

The chief manifestations of eclampsia—the rising blood-pressure, the albumin and casts in the urine, with the diminished urinary output, low urea output, and raised icteric index—are to be explained in the same way as in hyperemesis. The only difference is that they develop later in pregnancy. Perhaps this is due to sudden breakdown of the liver function, or to secondary kidney damage with its high arterial tension. In eclampsia:

"The capillary circulation throughout the body is slowed, the vessels showing greater permeability for water, which is retained in the tissues (hydrops). Oedema develops first in the legs, then eyelids and trunk, then in the brain, which explains headache and other cerebral symptoms." (Zangemeister[17].)

By means of the capillary microscope the constriction of the arterial half of the capillary loop may easily be seen, and when this phenomenon is very marked one can predict the imminence of convulsions (Nevermann). It is notable that "acute nephritis during pregnancy can seldom be distinguished from the glomerulo-nephritis or nephropathia of true eclampsia" (De Lee). In which fact one may possibly see a clue to the aetiology of Bright's disease, and the origin of the toxins which damage the kidneys.

It has often been stated that nothing is known about the nature of the toxins responsible for the pregnancy toxaemias. The tonsils, the cervix, the adnexa, the appendix, and the gall-bladder, have in turn been blamed. Dirmoser[14] blamed the alimentary canal. The most marked changes are found in the liver and kidneys, and Pinard[15] suggested that changes of the same kind as in hyperemesis and eclampsia and acute yellow atrophy are constant, in slight degree, in every pregnancy. He spoke of the "liver and kidney of pregnancy." If death occurs from hyperemesis it closely resembles that from "hepatic coma." It will be seen how well all these facts are to be explained by assuming the foetus to be the source of the toxins, further support being given by the increased incidence of hyperemesis and eclampsia with twins. Here we should expect the waste metabolic products of the two ova to be larger in amount, with correspondingly greater strain upon the liver of the mother. De Lee expresses the view, though he says he has no experimental confirmation to offer, that haemorrhagic diathesis, hyperthyroidism, nephrosis of pregnancy, apoplexie uteroplacentaire, hyperemesis and many other disturbances of pregnancy are due to incompatibility of the foetus with its mother. With this view the present author agrees, only substituting for the last phrase "inability of the mother to detoxicate in her liver the normal toxins produced by the foetus, so that they enter her general circulation through porto-renal and porto-caval anastomoses."

One other point must be mentioned. It is known that substances such as salts, potassium iodide, salicylic acid, morphia, methylene blue and arsenic acid, can pass through the placenta from the mother to the foetus. Similarly, if the portal toxins enter the circulation of the mother, they may pass through the placenta and cause the death of the foetus by convulsions truly eclamptic in nature. Such convulsions have been reported by Bar, Kapp, Dienst, and De Lee.[16]

Post-partum eclampsia. The occasional development of eclamptic fits only after delivery or death of the child, may be explained in the following way. The placental sinuses contain large quantities of venous blood saturated with foetal toxins, and the contraction of the empty uterus tends to force this blood into the maternal portal circulation. In a patient in whom the liver has been working to its utmost capacity right up to this moment, the sudden flooding of the portal system with further toxins in this way may prove too much for the over-taxed organ, and escape of the poisons into the general circulation will then result.

Habitual abortion and premature labour. It is obvious that eclampsia is only the climax of changes which have been taking place in the liver for weeks or months previously, e.g. in syphilis. It seems likely that in certain cases a degree of toxaemia not yet sufficient to cause eclampsia may bring about termination of the pregnancy by local damage to the placenta, which is of necessity specially exposed to the action of the toxins. Thus the condition of white infarct, and partial separation of the placenta may be regarded as due to direct poisoning of the placental cells.

Therapy of the toxaemias. It is always interesting to review the methods used in the treatment of a given condition, in the light of a new aetiological hypothesis. If methods which previously were empiric now become rational, support is given to the new theory. In the case of the pregnancy toxaemias, we may say that venesection would diminish the amount of circulating toxins, while colonic irrigation and a low fat and protein diet would help by minimizing the work devolving on the liver by reason of the mother's own alimentary processes. The most radical treatment, induction of labour, obviously cuts short the production of foetal toxins. According to the author's hypothesis, anything which might increase the work thrown upon the liver, such as the use of chloral or chloroform, would be contra-indicated.

The menstrual cycle. Why, if it is so important that the uterine venous blood should be carried to the liver during pregnancy, does not the uterus drain permanently into the portal system? The latter system is subject to rigid limitations; only the absorptive portions of the alimentary canal are included, the oesophagus and the anal canal belonging to the caval systems. It, therefore, seems quite in conformity that the uterus, the drainage of which is unimportant except during the reproductive period of life, and then only for relatively short intervals, should belong normally to the caval system. But it is an interesting possibility that with each menstrual cycle the first steps of the change-over to the portal system may occur, as preparation for a possible pregnancy, only to regress if this does not ensue. One may even speculate on a possible connexion between this circulatory change and the cyclical changes in the mucosa. If at the time of menstruation there exist enlarged communicating channels between the uterine veins and the portal system, some light is thrown on the very old belief that the menstrual discharges are poisonous.

The *rôle* of pituitrin is worthy of closer investigation. Since

this drug can act on veins, it may perhaps play some part in bringing about the diversion of the blood-flow, closing down one system at the expense of another; and possibly the phenomenon of vicarious menstruation could be linked with this conception: The whole question bristles with question marks, and the author has set forth his ideas in this paper in the hope of stimulating further enquiry and research.

TABLE I.

SOME ANASTOMOSES BETWEEN THE PORTAL AND THE CAVAL SYSTEMS.

(Modified from Thomas[3])

A. The Portal system communicates with the Superior Vena Cava:

By veins in the round ligament of the liver (para-umbilical veins), through superficial veins in the anterior abdominal wall to the internal mammary veins.

By deeper connexions between the para-umbilical veins and the superior epigastric veins.

By anastomoses between the left gastric vein and the oesophageal veins, which in turn connect with the intercostal veins, and so the azygos system.

Via the veins of Koelliker in the liver capsule, which connect the venous system (portal) of the lobules with superior diaphragmatic vessels, and so with the musculo-phrenics and finally the internal mammary veins.

By anastomoses between the splenic vein and the azygos system.

B. The Portal system communicates with the Inferior Vena Cava:

By connexion between the para-umbilical veins and the superficial epigastric veins, which enter the femoral veins.

By deeper connexion (veins of Burow) between the para-umbilical veins and the deep epigastrics, which open into the external iliacs.

By connexions between the left gastric vein and the inferior phrenic veins.

By connexions between the splenic vein (via the vasa brevia) and the left inferior phrenic vein.

By connexions between the pyloric veins and the right inferior phrenic vein.

By connexions between the splenic vein and the capsule of the left kidney (veins of Retzius).

SUMMARY

During normal pregnancy a physiological diversion of the venous blood stream from the caval to the portal system occurs. By about the twelfth week of pregnancy with the development of the new placental circulation the venous drainage of the pla-

centa, and therefore of the uterus, is diverted to the portal system and the liver, and the development of this diversion, with the enormous enlargement of the pudental plexus which it necessitates, causes the blueing of genitalia.

In toxaemia either the normal diversion of placental blood to the liver is delayed or imperfect, or there is some liver defect which impairs its detoxication function.

During pregnancy, and especially in hyperemesis gravidarum and eclampsia, the hypertension in the portal system may lead to a diversion of both maternal and foetal toxins direct into the kidney. Toxaemias are therefore due to the "inability of the mother to detoxicate in her liver the normal toxins produced by the foetus, so that they enter her general circulation through porto-renal and porto-caval anstomoses."

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The Treatment of Disproportion associated with a Moderate or Slight Degree of Pelvic Contraction in Primiparae

A Comparison between the Results Obtained by Instrumental Induction of Premature Labour, and the Method of Trial Labour

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A TRIAL of labour is the accepted treatment of to-day in cases of contracted pelvis of slight or moderate degree, in primiparous patients. The reasons which are commonly advanced in favour of trial labour, in place of induction of premature labour at, or after, the 36th week are:

1. That induction of premature labour in pregnancy is in a large number of cases performed unnecessarily in women who would, if left to undergo a labour at term, have delivered themselves spontaneously of living children.

2. That such interference by induction may be followed by sepsis or by haemorrhage and, therefore, these risks may be run unnecessarily.

3. Induction is by no means free from risk to the child. The foetal mortality reaches a high level when the forceps have to be used.

4. In a few cases Caesarean section has to be performed after instrumental induction, which, although disputed by some (Davidson,[1] Bethel Solomons and Wentworth Taylor[2]), is generally held to be dangerous to the mother.

5. The premature baby is considered by some to be difficult to rear. Provided, however, the induction is carried out at, or after, the 36th week, this is by no means universally accepted. (Johnstone,[3] Hunter,[4] Fletcher Shaw,[5] Wyatt.[6])

The above arguments seem satisfactory enough; but they do not take into account all the pros and cons of the problem. That there are certain disadvantages in trial labour even its most ardent advocates will agree. These may be summarized as follows:

First, there is what all must feel to be the catastrophe of a long and distressing labour, resulting in the birth of a dead child. There are few references in the literature to the importance of this occurrence, although there are some who believe that the psychological effect of this may be so profound as to make the woman unwilling to have another child. (Johnstone, Gordon Luker.[7]) The husband, too, may be unwilling, in these circumstances, for his wife again to become pregnant. Perhaps we are inclined to be a little too scientific in regarding the first child, in a young woman, as being the first, perhaps, of several children and, therefore, not of paramount importance. To the mother herself, the first pregnancy, the first labour, and the first child, is probably the most important of all her experiments in procreation.

Secondly, as Davidson points out, those clinics using the method of trial labour exclusively have a higher Caesarean section rate than clinics using induction methods. The Coombe Hospital Report for 1935 states:

"During last year we reduced the number of cases of induced labour. As a result, there has been an increase in the number of forceps cases and of Caesarean section."

It is the universal experience that, in the course of a trial of labour, a complete test cannot always be given. Many cases confront the obstetrician with uterine inertia, and premature rupture of membranes, and force upon him the employment of Caesarean section while the patient is still in the 1st stage of labour. Only too often do we find ourselves in the unenviable position of performing Caesarean section as an alternative to endangering the life of the child, while at the same time feeling that the operation may be unnecessary. Both Fairbairn[8] and Barris[9] stress the fact that unnecessary Caesarean sections may be performed in trial labour, in order not to risk the life of the child unduly.

After an analysis of 442 cases of prolonged trial labour (over 30 hours), Peckham and Kuder[10] advise lower segment Caesarean section when labour has lasted for 24 hours, with good pains, and with no signs of spontaneous delivery. They base this conclusion on the fact that the foetal mortality rises steeply after 30 hours, even if the delivery is eventually spontaneous.

It is known that the proportion of dead babies becomes less when the Caesarean section rate becomes greater, but it is unnecessary to stress here the disadvantages of Caesarean section

in a young primipara, both as regards its immediate and remote effects.

Granted that, in individuals, induction may be performed unnecessarily, is it not better, perhaps, to run this risk in order to avoid the catastrophe of a long labour, followed by a dead child, or a Caesarean section in a young woman?

There are modern developments in obstetrics which have benefited trial labour, in itself a modern treatment, but which have not been employed to any great extent in conjunction with induction of premature labour for contracted pelvis. Radiological investigations are the most important of these. Unnecessary inductions would probably be performed much less frequently if this method of treatment was only used in patients with proved pelvic contraction, showing the 1st degree of disproportion. At least, there would then be the satisfaction of knowing that the interference had been on account of a definite pathological condition. Moreover, it is possible that accurate knowledge of the size and shape of the pelvis, obtained both by clinical and radiological methods, would go far to reduce the failed inductions terminating in delivery by the forceps, which so often proves fatal to the child, or Caesarean section. Trial labour, or elective Caesarean section, would be used in selected cases.

In cases of contracted pelvis requiring induction, Hewitt[11] found that the results of puncturing the membranes with a catheter proved very favourable both to the patient and to the child. It seems that in the Drew Smythe catheter we have an instrument which, by high puncture of the membranes, will bring on labour efficiently, without the risk of "ladder infection" attendant upon the use of bougies, which were the commonly used means of inducing labour in the past (Browne,[12] Peel[13]).

There are two other points which are worthy of mention. The first is that the information obtained by observing the course of an induced labour is, in the opinion of many, of as great a value in foretelling the probable course of future labours as is that gained by the observation of a test of labour. (Fairbairn.)

The second has an important, if indirect, bearing on the subject. The teaching of methods of trial labour in medical schools may be misconstrued by some practitioners who, trusting to the trial of labour to solve their problems, may neglect to examine their patients thoroughly before labour commences. After a short and inadequate trial labour, these practitioners tend to lose confidence in their patients, and in themselves, and perform

what is, only too often, an unnecessary Caesarean section to end their difficulties; doubtless their minds are eased by the thought that the patient has had some sort of a test before the operation.

It is with the above points in mind that the writer has reviewed the literature, and has compared the results obtained by both methods of treatment, in a series of cases at University College Hospital, London.

Review of the Literature

Results obtained from Induction

There is, as might be expected, a very considerable literature on the results obtained by, and the problems of, instrumental induction of premature labour for contracted pelvis in primiparous women. On the other hand, the statistical evidence given as to the results of trial labour is smaller than one would expect.

Foetal and Neonatal Mortality.

Taking first the results of instrumental induction on the child, a good deal of difference is to be found in the figures quoted.

At one end of the scale there are foetal and neonatal mortalities of 4 per cent (Luker), 6.7 per cent (Johnstone), and 7 per cent (Davidson), and at the other end we find mortalities of 17 per cent (Wrigley[14]), and 20.8 per cent (Peel). The average combined foetal and neonatal mortalities, in the bulk of the literature, is quoted at 10.5 per cent to 12.5 per cent.

Maternal Morbidity and Mortality.

Regarding the effect of induction upon the mother, we find that the maternal mortality is very small. Bright Banister,[15] on analysis of 745 cases, recorded but 1 maternal death; Davidson had 1 death in 286 inductions; and Herbert Spencer maintained that large scale figures show a mortality of 0.2 per cent. In some papers, the maternal mortality is placed as high as one per cent but this high figure is only found when small numbers of cases are recorded. In other relatively small series of cases not any maternal deaths occurred. (Johnstone, Barris.)

The incidence of notifiable morbidity seems as variable as that of foetal mortality. The best results are given by Townend,[16] 1.5 per cent, and the worst by Peel, 18.8 per cent. The average

incidence seems to vary from 4 per cent to 8 per cent, in the literature as a whole.

The Forceps and Caesarean Section Rates.

The few references to the Caesarean section rate in induced labour place it at 5.6 per cent (Davidson) and 4 per cent (Hunter). The forceps rate in Peel's series is 35.8 per cent, and to this cause he largely attributes the high foetal and neonatal mortality already quoted. In Davidson's series the rate was 17 per cent. Other authorities do not seem to have used the forceps nearly as frequently as Peel, though few give definite figures.

As regards infantile mortality, we find that Johnstone traced 72 babies 2 years after induced delivery at or after the 36th week, and found that 87.5 per cent were alive and well. (Normal rate 87.8 per cent.) Twenty-seven cases remained untraced.

Lastly, Bright Banister recorded only an occasional incidence of haemorrhage following instrumental induction; and in the 745 cases he analysed, none of these haemorrhages was serious.

Results obtained from Trial Labour.

There are very few results of trial labour recorded in the literature. Hunter records a combined foetal and neonatal mortality of 14.3 per cent, with a Caesarean section rate of 33 per cent; while Robertson[17] puts the combined foetal death rate in hospital at 20—25 per cent. Peckham and Kuder state that while the foetal mortality rate in labours terminating in under 30 hours is 7.19 per cent, in more protracted labour this rate rises to 13.5 per cent with a maternal mortality rate of 1.36 per cent.

Other references to the literature have already been made in the first part of this paper.

Analysis of Cases at University College Hospital

Results obtained from Induction of Labour

There are 111 cases of induction of premature labour for contracted pelvis recorded at University College Hospital from 1921 to 1941.

These cases have been induced by bougies, or by bag, or by both methods, but the great majority by bougies. In some instances, drug inductions have been given in addition.

All the cases analysed have been induced from the 36th to 39th week inclusive, and only those patients who can be reason-

ably supposed to have contracted pelvis are included in the series. The degree of contraction in all cases was moderate or slight, with a conjugata vera of at least 3¼ inches, and at most 4 inches.

The induction was performed when 1st degree disproportion was present, and all the cases considered are primiparae.

Foetal and Neonatal Mortality.

There were 12 dead births, and one neonatal death, giving a total foetal and neonatal mortality of 11.7 per cent. Two dead births followed delivery by the forceps. Of the babies leaving hospital, all were in good condition on discharge.

There were not any Caesarean sections or craniotomies performed.

Maternal Morbidity and Mortality.

There was one maternal death due to septicaemia following induction. According to Spencer, this was the first maternal death following induction and delivered *per vias naturales* that has ever taken place in University College Hospital. Nine cases reached morbidity standard, giving a total morbidity rate of 9 per cent.

Spontaneous Delivery.

Delivery was spontaneous in 88.3 per cent with a foetal mortality of 11.2 per cent.

Forceps Rate.

There were 13 cases giving a forceps rate of 11.7 per cent, with a foetal mortality of 15.4 per cent. There were not any Caesarean sections.

Results obtained from Trial Labour

There are 57 cases of trial labour for contracted pelvis recorded at University College Hospital from 1932 to the commencement of 1941. A considerable number of trial labours for suspected disproportion are also on record, but the case-reports of these show that pelvic abnormality did not exist, and they have been discarded for the purpose of this investigation. The 57 cases analysed are those of patients who definitely had a contracted pelvis of moderate or slight degree. All the patients were primiparae, and the true conjugate was not greater than 4 inches, or less than 3¼ inches in any patient.

Foetal and Neonatal Mortality.

There were 8 dead births, and one neonatal death, giving a total mortality of 15.8 per cent. Two were delivered by Caesarean section, 3 by the forceps, 3 spontaneously, and there was 1 craniotomy.

Maternal Morbidity and Mortality.

There was 1 maternal death due to a cause entirely unconnected with the method of delivery. This followed an incompatable blood transfusion, given on account of post-partum haemorrhage.

Six cases reached morbidity standard, 4 of these patients were delivered by Caesarean section, 1 by the forceps, and 1 spontaneously. This gives a total morbidity rate of 12.3 per cent.

Spontaneous Delivery.

This occurred in 22 cases, that is to say in 38.6 per cent of the total number of cases. The foetal mortality rate in these cases was 13.6 per cent.

The Forceps and Caesarean Section Rates.

There were 11 cases by the forceps (19.3 per cent), with a foetal mortality of 27.3 per cent.

There were 23 Caesarean sections giving a rate of 40.3 per cent. In only 2 cases had the patient reached the 2nd stage of labour. The foetal mortality rate associated with Caesarean section was 8.7 per cent.

The explanation of the greater number of cases of contracted pelvis treated in 1921-31 as compared with the period 1932 to 1941 lies in:

1. The fact that some of the 1921 to 1931 cases were clinically diagnosed as contracted pelvis whereas, in fact, the pelvis was normal. In the period 1932 to 1941 more accurate methods of diagnosis (X-ray) excluded cases which might previously have been classed as contracted pelvis.

This bears out the writer's contention that X-ray pelvimetry is necessary in order to reduce the number of cases inaccurately classed as contracted pelvis. The effect of this should be to lower the number of unnecessary inductions.

2. The greater prevalence of contracted pelvis in the former period as compared with the latter (Rickets.) Such is indicated

TOTAL NUMBER OF CASES OF CONTRACTED PELVIS TREATED FROM 1921 TO 1931 (INDUCTION PERIOD) AND FROM 1932 TO 1941 (TRIAL LABOUR PERIOD—PRIMIPARAE)

1921 to 1931.	
Number of Caesarean sections for contracted pelvis ... ... (none following inductions)	29
Number of inductions for contracted pelvis	107
Total number of cases of contracted pelvis ... ... (induced or operated upon)	136
Caesarean section rate	21.3 per cent
1932-41.	
Number of Caesarean sections for contracted pelvis, with or without trial labour	38
Number of deliveries at term, *per vias naturales*, with contracted pelvis	34
Number of inductions for contracted pelvis	4
Total number of cases of contracted pelvis	76
Caesarean section rate	50 per cent

by the greater number of elective Caesarean sections from 1921 to 1941 (1921 to 1931, 29, and 1932 to 1941, 15, elective Caesarean sections).

3. The longer period from 1921 to 1931 (11 years) as compared with the period 1932 to early 1941 (9 years).

It is to be noticed that, despite the larger number of cases from 1921 to 1931 as compared with 1932 to 1941, the total number of Caesarean sections in the induction period falls considerably short of the total number performed during the trial labour period.

SUMMARY

The advantages of trial labour in the treatment of moderate or slight pelvic contraction, in primiparous patients, are:

1. Trial labour avoids unnecessary induction which may possibly be followed by haemorrhage or sepsis.

2. Trial labour avoids the risk of premature delivery with consequent high stillbirth and neonatal death rate, especially if the forceps have to be used.

The disadvantages of trial labour, in pelvic contraction of moderate or slight degree, in a primiparous patient, are:

1. The psychological effect upon the mother of the death of her first baby after a long and distressing labour.

2. The high Caesarean section rate and, in some cases, the performance of what might be unnecessary Caesarean section.

The use of X-ray pelvimetry, and perhaps the Drew Smythe catheter, might be expected to improve the results of induction, as obtained in the past.

Following a review of the literature, results obtained from an analysis of cases treated at University College Hospital are given, as below:

TABLE I.

	Number of cases	Foetal mortality rate	Maternal mortality rate	Maternal morbidity rate	Spontaneous delivery rate	Forceps rate	Caesarean section rate
		(per cent)		(per cent)	(per cent)	(per cent)	(per cent)
Instrumental induction	111	11.7	one case	9	88.3	11.7	Nil
Trial labour	57	15.8	one case	12.3	38.6	19.3	40.3

TABLE II.

	1921-1931	1932-1941
Total number of Caesarean sections	29	38

All the above were patients having a moderate or slight degree of pelvic contraction, the conjugata vera not being less than $3\frac{1}{4}$ inches in any of them.

Instrumental induction of premature labour was performed if 1st degree of disproportion occurred, and induction was not performed before the 36th week on any patient.

CONCLUSIONS

1. In the analysis of case records at University College Hospital, the results obtained by induction methods are more favourable than those obtained by trial labour (for direct comparison, see table presented in the Summary).

2. It is probable that an improvement upon the induction results of the past would be obtainable:

(*a*) By X-ray pelvimetry, added to the clinical estimation of pelvic contraction.

(*b*) By the use of the Drew Smythe catheter in the performance of the induction.

3. Induction of premature labour should be performed at, or after the 36th week, when clinical and radiological investigations show pelvic contraction with first degree of disproportion.

By keeping to the above ruling, labour would be induced for a proved pathological condition, when necessary, and when a successful delivery is probable.

4. Treatment by trial labour is indicated when pelvic contraction, but no disproportion, is present; or when there is suspected disproportion, but pelvic contraction cannot be demonstrated.

5. Treatment by elective Caesarean section should be reserved for those cases of contracted pelvis in which second, or greater degree of disproportion is present.

I am much indebted to Mr. Clifford White, Professor Browne and Mr. Norman L. White for their advice and for permission to make use of their case records.

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Vitamin E in Habitual Abortion and Habitual Miscarriage

BY

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IN 1931 Vogt-Möller[1] published the first report on the efficacy of vitamin E in the treatment of 2 cases of habitual abortion. He supplemented this with another in 1933[2] in which he reported the cases of 18 women who had habitually aborted, 89 per cent of whom had successful pregnancies on being treated with vitamin E. In 1936 he reported[3] 43 patients in whom 3 or more pregnancies had previously terminated between the 2nd and 7th month; these were similarly treated with vitamin E in later pregnancies, with favourable results ensuing in 70 per cent. Again, in a later paper at the Vitamin E symposium in England in 1939 he intimated[4] that his results were favourable in 75 to 80 per cent of a still larger series of such cases treated in this way.

In Canada, Watson and Tew[5] corroborated Vogt-Möller's findings, reporting the birth of 25 living babies in 35 women who had previously aborted, treated with vitamin E. Then Currie[6, 7] in England described in two interesting papers, success of about the same degree in the same type of troublesome case treated similarly. There have been other reports by Juhasz-Schäffer[8] McGonigle[9] and MacDonald[10] in the same vein. The only dubious voices to be heard have been the remarks of Bishop[11], Malpas[12] and the present writer[13]. It is important to note that Vogt-Möller's and Watson's and Tew's cases were not all personally studied by the authors.

Much of the problem resolves about the definition of habitual abortion and habitual miscarriage. The former remained comparatively undefined until the discussions of Whitehouse[14], Malpas[12] and MacGregor and Stewart[15] laid a sound statistical basis for such a definition—but they, like British writers in general, made no attempt to differentiate between habitual abortion and habitual miscarriage. American and Canadian authors usually refer by the term abortion to those pregnancies terminating at or before the 16th week of pregnancy, and by the term miscarriage to those pregnancies ending between the 16th and 28th weeks. If, as the author has claimed[16], [13] the fundamental func-

tion of vitamin E in pregnancy has to do with the efficiency of placental implantation, then there might be a good purpose to be served by separating the abnormal pregnancies under consideration here into two such groups, based on the well-known physiological change of the decidua basalis into placenta at about the 16th week of gestation.

Accordingly, with the observations of Whitehouse, Malpas, and MacGregor and Stewart in mind, let us define a woman who habitually aborts as of such constitution that she terminates about 75 per cent or more of her gestations spontaneously at or before the 16th week. Let us also understand in this connexion that she cannot be surely recognized as such until an abortion has happened at least 3 consecutive times, but that she possessed this habitus from the first; this is born out by the fact that her first abortion is as difficult to prevent as her second or third—which is not true of ordinary spontaneous abortions, as will appear in a subsequent publication. Similarly, a woman who habitually miscarries with an analogous constitutional habit except that about 75 per cent or more of her pregnancies tend to end spontaneously between the 16th and 28th weeks.

Based on these definitions, the problem assumes much different, but statistically correct, proportions. The data on true habitual abortion and miscarriage reported in the publications of the authors quoted above can now be summarized as follows:

TABLE I.

Author	Date	Number of true habitual aborters	Percentage of these women who preserved pregnancy after administration of E	Number of true habitual miscarriers	Percentage of these women who preserved pregnancy after administration of E
Vogt-Möller	1931	2	100	0	
Vogt-Möller	1933	17	88	1	100
Vogt-Möller	1936	43	70	?	
Juhasz-Schaffer ...	1933	5	100	0	
Watson and Tew ...	1935	35 (?)	71	?	
Currie	1936	4	100	8	100
Currie	1937	7 (?)	57	17 (?)	100
Bishop	1937	2	50	0	
Malpas	1938	6	33	0	
Cromer[17]	1938	1	100	0	
MacDonald	1939	18	94	0	
Lubin and Waltman[18]	1941	1	100	1	0
		141	76	27	96

NOTE: Only a few of these writers have given exact data on the time in pregnancy when the foetuses were expelled. Therefore, the distinction attempted above may not be quite accurate.

TABLE II.
Habitual Abortion.

Case	Pains	Bleeding	Therapy	Previous obstetrical record	Blood oestrin	Results
1	+	+	none	0	positive	6 weeks ab.
	+	+	w.g.o.	1 ab.	positive	6 weeks ab.
	+	+	w.g.o. + progesterone	2 ab.	positive	3 months ab.
2	?	?	none	0	positive	6 weeks ab.
	0	+	w.g.o. + thyroid	1 ab.	positive	4 weeks ab.
	0	+	w.g.o. + thyroid	2 ab.	not done	4 weeks ab.
	0	+	w.g.o. + thyroid	3 ab.	not done	2 months ab.
3	+	+	none	0	not done	8 weeks ab.
	+	+	w.g.o. + progesterone	1 ab.	positive	10 weeks ab.
	+	+	thyroid	2 ab.	not done	7 weeks ab.
4	0	0	none	0	not done	live, at term
	0	+	w.g.o.	1 child	not done	3 months ab. after otitis media and retinitis
	0	+	w.g.o.	1 child and 1 ab.	not done	7 weeks ab.
	0	+	w.g.o. and progesterone	1 child and 2 ab.	not done	10 weeks ab.
	0	0	w.g.o. to husband and wife and former off cigarettes, more sleep	1 child and 3 ab.	not done	live, term baby
5	0	+	none	0	not done	6 weeks ab.
	+	+	w.g.o.	1 ab.	positive	6 weeks ab.
	+	+	w.g.o.	2 ab.	positive	4 weeks ab.
	+	+	none	3 ab.	not done	3 months ab.
	0	0	Ephynal and husband's blood	4 ab.	not done	6 months pregnant
6	+	0	w.g.o.	0	positive	3½ months ab.
	+	+	w.g.o.	1 ab.	positive	3 months ab.
	0	+	w.g.o.	2 ab.	not done	2 months ab.
	0	0	w.g.o.	3 ab.	not done	6½ months anencephalic
	0	+	w.g.o.	3 ab. and 1 misc.	not done	2 months ab.
7	+	+	w.g.o.	0	negative	misc. at 4½ months
	+	0	w.g.o.	1 misc.	positive	tubal ab.
	+	+	Ephynal and husband's blood	1 misc., and 1 ab.	positive	5 weeks ab.

ab., abortion; misc., miscarriage; prem., premature; mac., macerated; s.b., stillbirth; w.g.o., wheat germ oil.

TABLE II (*continued*)

Case	Pains	Bleeding	Therapy	Previous obstetrical record	Blood oestrin	Results
8	+	+	none	0	not done	3 months ab.
	0	+	w.g.o.	1 ab.	not done	5 weeks ab.
	0	+	w.g.o. to her and husband	2 ab.	not done	7 weeks ab.
9	+	+	w.g.o.	0	positive	1 week ab.
	+	+	w.g.o.	1 ab.	not done	8 weeks ab.
	+	+	Ephynal	2 ab.	not done	6 weeks ab.
10	+	+	none	0	not done	3 months ab.
	0	0	none	1 ab.	not done	prolapsed cord, dead term child
	0	+	none	1 ab. and 1 child s.b.	not done	5 weeks ab.
	+	+	w.g.o.	2 ab. and 1 child s.b.	negative	3 weeks ab.
	+	+	w.g.o.	3 ab. and 1 child s.b.	positive	4 weeks ab.
11	+	+	w.g.o.	0	negative	6 weeks ab.
	0	+	w.g.o.	1 ab.	not done	3 weeks ab.
	+	+	w.g.o.	2 ab.	not done	4 weeks ab.
	+	+	Ephynal and progesterone	3 ab.	not done	8 weeks ab.
12	?	?	none	0	not done	6 weeks ab.
	?	?	none	1 ab.	not done	7 weeks ab.
	?	?	none	2 ab.	not done	7 weeks ab.
	0	0	w.g.o.	3 ab.	not done	term live baby
13	?	?	none	0	not done	2½ months ab.
	0	+	w.g.o.	1 ab.	negative	6 weeks ab.
	0	+	w.g.o.	2 ab.	not done	6 weeks ab.
	0	0	none	3 ab.	not done	term live baby
14	?	?	none	2 children	not done	3 months ab.
	?	?	none	2 children and 1 ab.	not done	3 months ab.
	?	?	none	2 children and 2 ab.	not done	4 months ab.
	0	0	w.g.o.	2 children and 3 ab.	positive	term live child
15	0	+	w.g.o.	abs.?	negative	6 weeks ab.
	0	0	w.g.o. and progesterone	1 + ab.	not done	5 weeks ab.
	0	0	w.g.o. and progesterone	2 + ab.	not done	3 weeks ab.
16	?	?	none	1 child	not done	3 months ab.
	?	?	none	1 child and 1 ab.	not done	2 months ab.
	?	?	progesterone	1 child and 2 ab.	not done	5 weeks ab.
	+	+	Ephynal	1 child and 3 ab.	not done	2½ months ab.
17	0	+	none	0	not done	3 months ab.
	0	+	w.g.o.	1 ab.	positive	2 months ab.
	+	+	w.g.o.	2 ab.	not done	6 weeks ab.
	?	?	Lugol's iodine	3 ab.	not done	live term baby

TABLE III.

Habitual Miscarriage.

Case	Pains	Bleeding	Therapy	Previous obstetrical record	Blood oestrin	Results
18	0	0	none	0	not done	28 weeks' baby, lived 3 days
	0	0	none	1 prem.	not done	therapeutic ab. for vomiting
	0	0	none	1 prem. and 1 ab.	not done	misc. at 24 weeks, baby lived 10 minutes
	0	0	none	1 prem., 1 ab., and 1 misc.	not done	11 weeks ab., twins
	0	0	progesterone and insulin	1 prem., 2 ab., and 1 misc.	not done	misc. at 24 weeks
	0	0	progesterone	1 prem., 2 ab., and 2 misc.	not done	prem. at 28 weeks; it died
	?	?	w.g.o.	2 prem., 2 ab., and 2 misc.	positive	6 weeks ab.
	0	0	husband's blood every 3 days	2 prem., 3 ab., and 2 misc.	not done	live term baby
19	0	0	none	0	not done	normal child at term
	0	0	none	1 child	not done	1 s.b. at term
	0	0	none	1 child and 1 s.b.	not done	misc. at 6 months
	0	0	none	1 child, 1 s.b., and 1 misc.	not done	6 weeks ab.
	0	0	w.g.o. and progesterone	1 child, 1 s.b., 1 misc. and 1 ab.	not done	prem. at 7 months; did not live
20	0	0	none	0	not done	therap. misc. at 7 months
	0	0	none	1 misc.	not done	misc. at 6 months
	0	0	none	2 misc.	not done	misc. at 6 months
	0	0	w.g.o.	3 misc.	not done	live term baby
21	0	0	none	0	not done	prem. child, lived
	0	0	bed	1 child	not done	6 months misc.
	+	+	none	1 child, 1 misc.	not done	3 months ab.
	0	0	w.g.o.	1 child, 1 misc., and 1 ab.	negative	6 months misc.
22	0	0	none	0	not done	7 months mac.
	0	+	none	1 prem, mac.	not done	3 months ab.
	0	0	none	1 prem. and 1 ab.	not done	6 months misc.
	0	0	w.g.o.	1 prem., 1 ab., and 1 misc.	not done	7½ months mac.

ab., abortion; misc., miscarriage; prem., premature; mac., macerated; s.b., stillbirth; w.g.o., wheat germ oil.

In general, it may be said that the dosage used by various writers has often been so small that one fails to understand how it could have been genuinely helpful. It will be seen from this table that when habitual abortion has been differentiated from habitual miscarriage the results in the latter have been much the better on E-therapy. As "habitual abortion" has been suggested as the principal indication for the use of E, it is not surprising that it has failed to obtain enthusiastic acceptance up to this time. Its failures in this field have militated against its use in others where it has proved much more valuable[13].

The writer's experience is summarized in Tables II and III.

Summarizing these tables in 5 of these 17 women who had been the victims of true habitual abortion finally succeeded in producing live children at term and one has brought her foetus to viability (35 per cent successes). This figure agrees fairly well with the results given by Malpas and those of Currie's second paper. Three out of 5 women who had true habitual miscarriages had live children at term (60 per cent successes).

Better success, therefore, was achieved in the miscarrying than in the aborting women. But when this data is analysed further, as follows, it presents no clear argument favouring the use of vitamin E in habitual abortion, at least. Moreover, the earlier in pregnancy the habit shows itself, the more hopeless the outlook seems to be.

Analysis of Successful Cases

Case 4. There had been an initial normal pregnancy. Then 3 successive pregnancies had terminated in abortion when she was taking huge doses of wheat germ oil. She took it in her final successful effort too, but in the latter, the husband, an overworked physician, underwent some preparation before the pregnancy occurred.

Case 5. Two previous abortions had not been prevented by vitamin E. She presented herself this last time when she was much further advanced in pregnancy than she had ever gone before, and she had had no treatment up to that date. She did not display any evidence of E-deficiency in this pregnancy, and, although she has been given E ever since she was first seen, it is doubtful if it is helping her carry this pregnancy so easily.

Case 12. Success in this case might or might not be ascribed to vitamin E.

Case 13. This woman aborted twice on large doses of E and carried to term when taking none.

Case 14. Success here might or might not be ascribed to vitamin E.

CASE 17. This patient had aborted time after time despite huge doses of wheat germ oil. Finally she went to another obstetrician who prohibited the oil on account of its toxic (!) effect, put her on Lugol's iodine, as she had had a previous thyroidectomy, and she had a fine baby. The very experienced surgeon who had performed her operation had not thought she needed Lugol's iodine, although she had seen him repeatedly after her operation.

CASE 18. This woman, a doctor's wife, had consulted two of the leading endocrinologists in the United States regarding her habitual miscarriage, and the severe vomiting which accompanied each pregnancy. Both had told her she exhibited oestrogen deficiency, and treated her accordingly—without success. She presented so many features of hypothyroidism that oestrogen excess seemed much the more logical thing to expect, and a blood test in a later pregnancy confirmed this. She was put on vitamin E, but aborted almost as soon as it was instituted. In her last and successful pregnancy the husband paid no further attention to hormone or vitamin therapy, but, finding that he and she were of different blood groups, injected her intramuscularly at least once a week with his own blood during her pregnancy. This management was successful.

CASE 20. The success of the treatment might or might not be ascribed to vitamin E.

CASE 22. The same might be said of this patient.

It should be stated that all these women were given very large doses of wheat germ oil (Kelly's) or of α-tocopherol acetate (Ephynal—Hoffman La-Roche). The daily doses range from 2 to 5 tablespoons of the former and from 20 to 50 mgm. of the latter.

This small series of personally observed private patients cannot prove or disprove the value of vitamin E in the treatment of habitual abortion or habitual miscarriage, but the experiences here summarized explain why the writer is dubious of its efficacy for habitual abortion, at least. It should be added that early habitual abortion, as distinct from habitual miscarriage, seems to be not uncommon, at least in this part of North America. Many "menstruations" are really early abortions, and many of the most hopeless cases of "sterility" turn out to be really those of habitual early abortion.

SUMMARY

1. The literature on habitual abortion and habitual miscarriage is reviewed, with especial reference to the need for a strict definition of these two terms.

2. A definition is offered.

3. A series of 17 women who had true habitual abortions and 5 women who had true habitual miscarriages is described in tabular form, giving brief details of all their pregnancies both before and during treatment with vitamin E or other agents.

4. A discussion of the results obtained does not offer any convincing evidence that vitamin E, even when given in large doses, is of definite value in the treatment of habitual abortion, as distinct from habitual miscarriage. It may be helpful in the latter.

The writer desires to thank the Kelly Laboratories of London, Canada, and Hoffman La-Roche, Montreal, Canada, for the vitamin E used in this study. He should also express his gratitude to several physicians, whom he leaves unnamed, for their co-operation.

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Pregnancy Following the Intra-uterine Application of Radium

BY

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THE use of radium to produce an artificial menopause in patients suffering from uterine haemorrhage of non-malignant origin is a procedure which is recognized to give highly satisfactory results. There is less agreement concerning its value in younger women affected by similar conditions; the main argument centres round the likelihood of the restoration of a normal menstrual rhythm, but its value must also be assessed by the effect on subsequent conception, pregnancy and parturition. While it has often been demonstrated that normal menstruation can be restored, and there are isolated reports of normal and abnormal labours after intra-uterine radium, the literature does not contain any account of the proportion of such women who become pregnant, and the course of their labours.

REVIEW OF THE LITERATURE

Schmitz,[1] Dawson,[2] and Rouffart Marin[3] each report a case of normal pregnancy and labour after intra-uterine radium. Keene and Payne[4] give the results of radium treatment in functional uterine bleeding, and mention that in 120 women aged 40 years or less, receiving 200 to 500 mgm. hours, there occurred 23 pregnancies, 12 of these ending in miscarriage, and 11 patients produced living children. Details are not given of the labours, nor in the case of the miscarriage is the duration of the pregnancy stated. Kelly[5] reports the only other series in the literature. He found that of 30 patients, aged 13 to 25, who received doses averaging 538 mgm. hours, 4 became pregnant. One patient had 2 normal pregnancies and one stillbirth, while the others miscarried at 3, 4½, and 5 days respectively.

Kane[6] records 6 labours following previous radium therapy in which the cervix failed to dilate. One case was a 6 months' abortion with an undilatable cervix treated by removal of the

unopened uterus. The other 5 patients went to term or the pregnancies were post-mature. One was delivered of a living child by Caesarean section, but in the remaining 4 the foetal heart sounds ceased before or during labour. One patient was delivered vaginally after a difficult craniotomy, the other 3 were delivered abdominally, Porro's operation being performed twice. The mothers all survived after varying degrees of stormy convalescence. Anderson[7] records a case of pregnancy 3 years after an intra-uterine application of 1080 mgm. hours of radium. At the end of the 7th month the foetus died *in utero*, and labour began after the membranes had been ruptured for one week. The cervix failed to dilate and Caesarean section had to be performed. The puerperium was septic but the patient recovered. Ridler[8] records the case of a multipara pregnant 3 years after the intra-uterine injection of 1080 mgm. hours of radium. When the patient was one month post-mature the membranes ruptured as a result of repeated drug inductions. The cervix was manually stretched and a foot pulled down, but although pains were strong there was not any progress during 3 days. Finally Caesarean hysterectomy was performed.

In the series now published an attempt has been made to follow-up patients below the age of 40 treated for menorrhagia by radium in the Royal Free Hospital between the years 1927 and 1937. The radium was used in tubes, the screenage being 1 mm. of platinum and a rubber covering. Eighty-nine patients were traced, and 9 of them had between them 14 pregnancies. In addition to the description of these labours 2 others from a different source are added in the discussion which follows.

Case Histories

Case 1, Mrs. B. This patient, a 1-para, aged 28, was given in 1930 an intra-uterine application of 50 mgm. radium for 22 hours (1100 mgm. hours). She became pregnant 4 years later, went into labour at term, and was delivered spontaneously of a healthy child. She has not become pregnant again, although anxious to do so.

Case 2, Mrs. D. In 1932 this patient, a 7-para, aged 32, was given an intra-uterine application of 50 mgm. radium for 22 hours (1100 mgm. hours), and this restored normal menstruation. She has since had 3 pregnancies. The first in 1935 ended in abortion during the 3rd month, the second, in 1938, ended in abortion during the 5th month. On both occasions it was necessary to complete the evacuation of the uterus under anaesthesia. She became pregnant again shortly afterwards, and this time her pregnancy lasted until the 8th month when she was admitted to hospital with ruptured

membranes. The foetus was small and presented by the breech, and labour lasted 5 days because of cervical rigidity. During delivery the foetal head became arrested as the result of incomplete dilatation of the cervix, and was extracted after considerable delay, the child being stillborn. Free haemorrhage followed bilateral tearing of the cervix which was repaired under general anaesthesia. The puerperium was febrile from local uterine infection, but the patient was discharged one month later in good condition.

CASE 3, Mrs. G.G. In 1932 this patient, a 2-para, aged 36, was given an intra-uterine application of 50 mgm. radium for 18 hours (900 mgm. hours). She has become pregnant twice; once in 1938 when she aborted at the 3rd month and again in 1939 when she aborted at the end of the 4th month.

CASE 4. Mrs. F. In 1932 this patient, a 1-para, aged 30, received an intra-uterine application of 50 mgm. radium for 12 hours (600 mgm. hours). She became pregnant 4 years later and carried her pregnancy to term. Labour was prolonged on account of slow dilatation of the cervix, and she was delivered after 3 days of a stillborn child. The puerperium was pyrexial due to an infection of the genital tract.

Menorrhagia returned after the confinement, and in April 1938 hysterectomy was considered, but in view of the patient's great desire for a living child, dilatation and curettage were performed as a palliative measure. She is now 5 months pregnant and so far has remained well.

CASE 5, Mrs. N.G. In 1928 the patient, a nullipara, aged 19 years, received an intra-uterine application of 100 mgm. radium for 24 hours (2000 mgm. hours). Following this the menstruation remained on the whole regular, though there was sometimes a 6 weeks' interval between periods. She subsequently married, and returned to hospital in September 1936, after 7 months' amenorrhoea, and the uterus was found to be enlarged to the size of a 14 weeks' pregnancy. Foetal movements were felt 6 weeks later, and the antenatal period progressed normally until the end of December. She was then admitted to hospital with ruptured membranes and some vaginal bleeding. The uterus was enlarged to the size of a 32 weeks' pregnancy, the child presented by the shoulder and the foetal heart could not be heard. On vaginal examination the cervix admitted one finger, and placental tissue could just be reached posteriorly encroaching on the lower uterine segment. The cervix was stretched to admit a second finger, bipolar version was performed and a leg brought down. The bleeding was controlled, labour pains started and continued at regular intervals. After 60 hours the breech began to advance, the legs and trunk of a macerated foetus were expelled and progress then ceased. Vaginal examination showed that delay was caused by the cervix which was contracted tightly round the neck of the child. All attempts to dilate the cervix manually, or with drugs, failed and the head was perforated and extracted some hours later with much difficulty. The 3rd stage of labour and the puerperium were normal.

CASE 6, Mrs. E.J. In 1932 this patient, a 2-para, 31 years old, received an intra-uterine application of 25 mgm. radium for 30 hours (750 mgm.

hours). She became pregnant in 1938 but aborted at the end of the 3rd month.

CASE 7, Mrs. M. In 1932 this patient, a 4-para, aged 38, was given an intra-uterine application of 50 mgm. radium for 22 hours (1100 mgm. hours). Her periods were normal for 15 months and then became profuse. For a month before her second admission she had continuous bleeding with two profuse haemorrhages. Panhysterectomy was performed, and when the uterus was cut open, a large, black, foul-smelling tumour was found at the junction of the cervical canal with the body of the uterus, which proved on microscopical examination to be a chorion carcinoma.

CASE 8, Mrs. R.S. In 1930, at the age of 14, the patient was given an intra-uterine application of 25 mgm. radium for 12 hours (300 mgm. hours) for menorrhagia of puberty. Following this the menstruation returned to normal. Four years later she married, became pregnant, and remained well throughout the antenatal period. On September 3rd, 1935, she was seen at the clinic, being then 14 days beyond the expected date of delivery. The child presented by the vertex and the foetal head was floating freely above the pelvic brim, though the capacity of the pelvis was normal. She was admitted to hospital 3 days later for medicinal induction of labour, and on September 6th was given castor oil, 3 doses 10 gr. quinine sulphate, at hourly intervals, and pitocin 2.5 units also three doses at hourly intervals. Labour began after the last dose of pitocin and 5 hours later at 4.45 p.m. the membranes ruptured discharging a quantity of liquor stained with meconium. By 9 p.m. the uterine contractions were extremely powerful, recurring frequently and lasting 2 to 3 minutes, although the uterus relaxed between the pains. As the foetal head had not yet entered the pelvis, the patient was prepared for Caesarean section but at 9.35 p.m. she suddenly had a tetanic fit and died. All efforts to resuscitate the mother failed but a live child was extracted by post-mortem Caesarean section. Post-mortem examination of the mother showed the cause of death to be acute heart failure, and disclosed an incomplete rupture of the uterus on the right side, three-quarters of an inch long at the junction of the upper and lower segments. The cervix was thick and only dilated to admit 2 fingers. Unfortunately a microscopical examination was not made as neither the pathologist who made the post-mortem nor those who supervized the labour were aware of the previous application of radium.

CASE 9, Mrs. W. In 1929, this patient, a 1-para, aged 39, was given an intra-uterine application of 50 mgm. radium for 22 hours (1100 mgm. hours). She had two miscarriages at the 3rd month, the first in 1930, the sencond in 1933.

DISCUSSION

There are three aspects of the subject which call for discussion. These are the fertility rate, the abortion rate, and the incidence of difficulty in labour.

Nine of the 89 patients traced became pregnant, which gives

a fertility rate of 10 per cent corresponding closely with the figure of 12 per cent quoted by Keene and Payne. The lower fertility and the high abortion rate must not be attributed solely to irradiation, for all of these patients had previously some pathological lesion which may have itself retarded conception or led to imperfection in embedding of the ovum. It is usually stated that the smaller doses of 600 mgm. hours or less may be followed by pregnancy while larger doses lead to permanent sterility. In this series this has not been the finding, for the patients who subsequently became pregnant had received doses of 1100, 1100, 900, 600, 2000, 755, 1100, 300 and 1100 mgm. hours respectively. Two patients had not borne children before irradiation, the other 7 were multiparous. The interval elapsing between the application of radium and subsequent pregnancy did not bear any relation to the dose employed, nor to the parity of the patient.

Eight of the 14 pregnancies ended in abortion. The average duration of gestation was 14.6 weeks, the actual period of gestation being 12, 22, 12, 19, 15, 12, 12, and 12 weeks respectively. The viable children were born 4, 5, 4, 8, and 5 years after irradiation. The abortions occurred on the average $4\frac{1}{2}$ years after treatment, the times being 3, 6, 6, 7, 6, 2, 2, 5 years respectively. The cause of these abortions is difficult to determine; possibly scar tissue in the uterus and lower segment is responsible, they would in such a case be similar to the abortions that commonly follow high amputation of the cervix.

The third point arising, and possibly the most important, is dystocia during labour from delay in dilatation of the cervix. In cases 2, 4 and 5, each of which the delivery was by a different obstetrician in a different hospital, cervical rigidity was the feature spontaneously stressed by the accoucheur. In case 8 the failure of the foetal head to advance was not well understood at the time, as the child weighed only 6 pounds, its presentation and attitude were normal, and the pelvic capacity adequate. It is, therefore, at least possible that the head was held up by a cervix which, failing to dilate, led to rupture of the uterus.

In this connexion it may be of interest to report 2 further obstetrical cases seen by the author, in which delay in dilatation of the cervix complicated labour after the application of intra-uterine radium.

CASE 10, Mrs. M. This patient, a nullipara of 28 years, received an intra-uterine application of radium for 12 hours (300 mgm. hours). She became pregnant the following year and, though having a slightly raised

blood-pressure, remained well throughout pregnancy. She was admitted to hospital at the 38th week in labour and with ruptured membranes. The child presented by the breech, the foetal heart was heard, and the cervix had dilated to admit four fingers. Eighteen hours later the breech began to advance, the lower limbs and trunk were born spontaneously. After the arms had been delivered the descent of the foetus became arrested and a hand passed into the vagina found a thick ring of cervix gripping its neck. The patient was given morphia and a weight of 2 pounds was attached to the legs. This had no effect on the cervix and 10 hours later the foetal head was perforated and extracted. The patient died 2 days later, death being due to multiple pulmonary infarction.

Case 11, Mrs. A.M. This patient, a 3-para, aged 36, received an intra-uterine application of 36 mgm. radium for 22 hours (1100 mgm. hours). She became pregnant 2 years later and was well during the antenatal period. She was sent to hospital when one month post-mature because foetal movements had ceased. The foetal heart could not be heard, and radiography showed collapse of the foetal head. Medical induction was unsuccessful and the patient went into labour spontaneously 8 days later. After 16 hours of pains the head was delivered easily and without aid, but the shoulders failed to advance in spite of strong pains combined with traction on the foetal head. A hand passed up found the cervix gripped tightly round the child's neck. The patient was given omnopon gr.⅓ and left for an hour. She was then anaesthetized deeply and the shoulders extracted with difficulty after cleidotomy. There was local uterine sepsis and delayed involution during the puerperium, but the patient was discharged in good condition 3 weeks after delivery.

Summary

1. A series of 89 patients under 40 years of age, who had been treated with an intra-uterine application of radium for non-malignant conditions, have been studied to determine frequency of conception after treatment, and the course of their pregnancies.

2. Nine of the patients subsequently became pregnant and had between them 14 pregnancies. Abortion occurred in 57 per cent of these pregnancies, and in only 5 cases did the foetus attain viability. One patient is still pregnant.

3. In the whole series, and out of 14 pregnancies, only 2 live children were born. The cause of this wastage was first the high incidence of abortion, and secondly dystocia during labour.

4. Severe dystocia may result from delay in the dilatation of the cervix in cases in which an intra-uterine application has been made. Six such cases are described. The cause of the dystocia was cervical fibrosis. Whether it can be avoided by using only a short intra-uterine tube and confining the irradiation to the top half of the uterus is a point worthy of consideration.

ACKNOWLEDGMENTS

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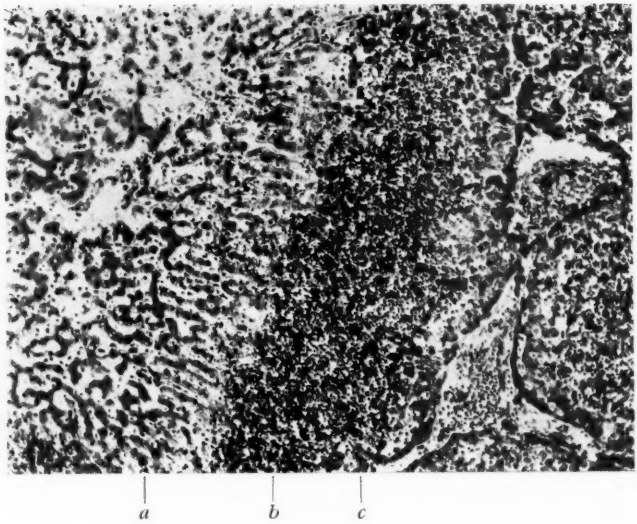
PLATE I.

Liver showing mid-zonal necrosis.



Low power.

a Surviving centro-lobular cells showing some fatty change

b Mid-zonal band of necrotic cells

c Surviving peri-portal cells

Clinical and Biochemical Findings in Delayed Chloroform Poisoning

BY

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CASES of delayed chloroform poisoning are occasionally met with in the puerperium. Gibberd[1] reports 3 fatal cases and gives a review of the literature on this subject and an excellent account of the clinical aspects of the disease. Sheehan[2] has laid stress on the fact that, when a patient has much vomiting during labour or has been left in labour for an exceedingly long time, the resultant metabolic disturbances make her specially susceptible to delayed chloroform poisoning if this anaesthetic is given for the delivery. He has pointed out that the liver lesion in these dystocia cases is a mid-zonal necrosis which spreads centrally in severe cases, and has shown how this differs from the centrolobular liver lesions which are produced by giving chloroform to patients with hyperemesis.

The present paper deals with 3 very severe but non-fatal cases and 2 milder cases of delayed chloroform poisoning which have been the subject of a clinical and biochemical study.

CLINICAL ASPECTS

In each of the severe and in one of the mild cases there was the very typical story that the chloroform was given for the delivery after the patient had been in labour for a long time; the mean length of labour for the 4 cases was 52 hours. Vomiting had occurred frequently during labour in all cases. These 4 patients were, therefore, dehydrated, acidotic and uraemic before the anaesthetic was begun. In 2 of them an attempt had been made to protect the liver by the administration of 600 c.c. of 30 per cent glucose intravenously; one at half an hour before the anaesthetic and the other during it. These attempts at prophylaxis appear to have been too late to be successful. The other mild case was an eclamptic treated by the Strogonoff method. Chloroform was given for a few minutes on four different occasions during and after labour. Labour lasted 24 hours

and delivery was spontaneous. This was the only eclamptic patient, out of a very large series treated by the Strogonoff method, who showed any evidence of chloroform poisoning.

The clinical course of the disease in the severe cases was as follows: the patients vomited occasionally during the first 2 days of the puerperium and on the 2nd or 3rd day they were noticed to be slightly jaundiced. The temperature and pulse-rate remained within normal limits for about 48 hours after the administration of the chloroform and then rose suddenly—temperature 99°F. to 101°F. and pulse-rate at about 120 per minute. On the 3rd day post-partum each patient became acutely ill. Vomiting was more frequent and there was some abdominal pain with tenderness over the liver. The jaundice deepened rapidly and the patients became restless and later delirious; 2 of them were completely comatose by the 4th day post-partum. At this time the temperature ranged from 103°F. to 105°F. and the pulse was very weak and rapid—often over 160 per minute. The urine contained much bile pigment and the faeces were of normal colour; the skin was deeply jaundiced. Continuous drip intravenous transfusions were given from the 3rd day post-partum, starting with about 300 c.c. of 50 per cent glucose and following on with 500 to 1000 c.c. of 20 per cent glucose, and finally 5 per cent glucose saline. The 300 c.c. of 50 per cent and 500 to 1000 c.c. of 20 per cent glucose were repeated every 12 hours and small doses of insulin (5 to 10 units) were given along with the glucose. The total amount of intravenous fluid given was about 10 litres. Slight improvement (fall in temperature and pulse-rate and signs of returning consciousness) began on the 5th day post-partum. On the 6th day the patients had regained consciousness but were very weak. There was no sickness and the intravenous therapy was stopped. The temperature and the pulse-rate fell gradually to reach normal levels by the 8th day post-partum. The jaundice remained unchanged till the 6th or 7th day post-partum, when it began to diminish; slight icterus persisted for about 2 weeks.

In the mild cases there was only slight vomiting; jaundice appeared on the 2nd day post-partum but lasted only a few days and mental symptoms were absent.

Biochemical Aspects

The biochemical findings throughout the course of the disease in each case have been followed. Graphs of the mean changes of the various substances in the blood in the 3 severe

CHART I

CHANGES IN HAEMATOCRIT AND PLASMA BILIRUBIN

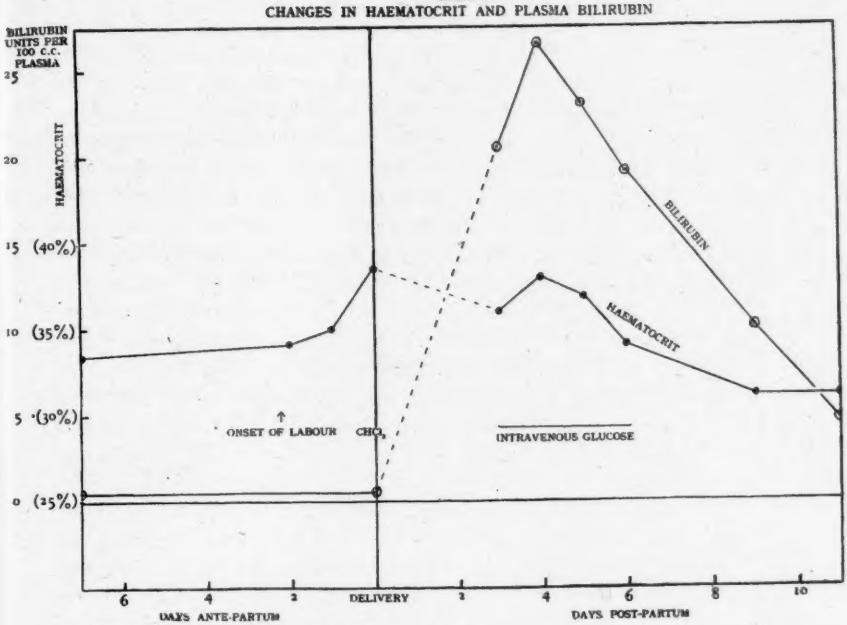
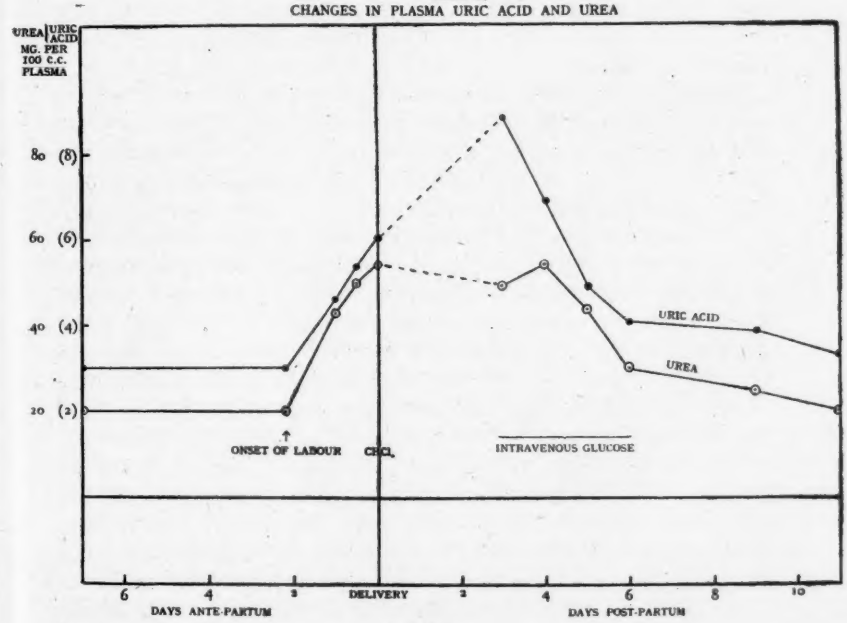


CHART II

CHANGES IN PLASMA URIC ACID AND UREA



cases are given in Charts I and II. Investigation of these cases was not started until the 3rd day post-partum and therefore the levels of the substances immediately after delivery are not precisely known. Nevertheless it is possible to estimate them at that time with reasonable accuracy. The changes in blood concentration during labour, as measured by the haematocrit, have been studied previously (Crawford[3]). It has also been shown that labour causes a retention of non-protein nitrogen fractions in the blood, the degree of the retention being proportional to the length of the labour (Crawford[4]). From the data in these papers the standard changes in the haematocrit, plasma uric acid, urea and bilirubin in a patient with a 52-hour labour are shown in Charts I and II from 7 days ante-partum till delivery. In both charts the levels of the various substances in the present cases during the first 3 days post-partum have been interpolated (dotted lines).

The course after the 3rd day post-partum may be considered under three headings.

Haematocrit. The mean haematocrit value in the delayed chloroform poisoning cases is relatively high. The fall in haematocrit values, which normally occurs during the first 3 days post-partum, did not take place. After the 4th day post-partum there was a decrease in haematocrit values and this was accompanied by signs of improvement in the clinical condition.

Bilirubin. In each case the plasma gave a delayed direct reaction to the Van Den Bergh test on the 3rd day post-partum and the plasma bilirubin was very high (24 to 32 units). The plasma bilirubin values began to fall after the 4th day post-partum but were still above normal limits at 12 days post-partum.

Plasma uric acid and urea. The plasma uric acid and urea values in these cases did not show the rapid fall usually found during the first 3 days post-partum after a prolonged labour. The plasma uric acid level actually showed a very marked rise during this time; the mean value for the 3 cases on the 3rd day post-partum was 8.8 mgm. per 100 c.c. plasma. A considerable decrease in the uric acid values had occurred by the 4th day and this decrease continued till the 12th day post-partum when normal levels were regained. The plasma urea values, on the other hand, showed a slight fall during the first 3 days post-partum followed by a rise on the 4th day. After the 4th day post-partum the urea values fell in proportion with the uric acid values. The fall in the uric acid level began, in each case, at least 24 hours before there was any other biochemical or clinical sign of im-

provement; apart from this, however, the plasma uric acid and urea values followed the haematocrit changes.

The typical histological changes may be illustrated from a case of delayed chloroform poisoning in which the patient died from a combination of this and of shock following delivery. She had been given chloroform for 20 minutes on two occasions. Moderately severe vomiting had been present for 48 hours before the first administration of chloroform and this sickness continued during the next day when labour began. Vomiting was severe and the patient was very acidotic. Chloroform was again given for the delivery after a 4-hour labour. The child was delivered by the breech and weighed 6¾ pounds. The patient's condition after delivery was very poor. She died 6 hours post-partum and about 72 hours after the first administration of chloroform; this was clearly the administration that produced the liver lesions. The blood urea at death was 26 mgm. per 100 c.c. plasma. At the autopsy the liver weighed 1,220 gms.; the cut surface was pale and mottled by tiny red lines which encircled each lobule near the periphery. Microscopically there was a very definite mid-zonal band of necrosis with some haemorrhage and early polymorph infiltration into it and there was fatty degeneration of the centrolobular cells. (Plate I.)

Discussion

The clinical findings in the present cases are essentially similar to those described by Gibberd but there are one or two points requiring further emphasis and explanation. In the first place, the great importance of the pre-anaesthetic acidosis, due to prolonged labour and/or severe vomiting, has not yet been fully realized although stressed by Royston[5] and Sheehan. It is of interest to note from the present cases that 600 c.c. of 30 per cent glucose given intravenously half an hour before the anaesthetic did not prevent the liver damage.

A second feature of the disease which has not been fully recognized is the occurrence of a 'crisis' on the 4th or 5th day after the administration of chloroform. In practically all the fatal cases reported (Stander[6]; Royston, cases 1 and 3; Stander[7]; Gibberd, cases 2 and 3; Sheehan, 9 cases) death occurred before or on the 5th day. Gibberd's first case is an exception but in this case some other factors seem to have been present. From a study of the present cases and of other non-fatal cases of delayed chloroform poisoning reported in the literature (Royston, case 2; Townsend[8], case 2), it would appear that, if

a patient survives for over 5 days after the injury by chloroform, recovery can be expected; unless, of course, other factors are present which may of themselves cause death—such as infections of the uterus or kidneys.

The biochemical findings in the present series are of some interest. Stander found moderately raised blood urea and very high plasma uric acid in his cases, but in Gibberd's cases the blood urea rose rapidly to very high levels at death. In the present cases the changes in the blood urea levels are slight and vary with the haematocrit changes; they can probably be wholly accounted for by the effect of labour and the changes in blood concentration. In the fatal case with a labour of 4 hours the blood urea at death was only 26 mgm. per 100 c.c. Soffer, Dantes and Sobotka[9] studied the changes in the blood chemistry of dogs following hepatic injury with intravenous arsphenamine and they found marked haemoconcentration with a rise in non-protein nitrogen and urea. From a study of their results from individual dogs it can be seen that the non-protein nitrogen retention was roughly proportional to the increase in haemoconcentration; in two dogs that did not show any haemoconcentration there was no rise in the blood non-protein nitrogen.

The plasma uric acid values in the present cases show much greater changes than the urea values. Bollman, Mann and Magath[10], and Gremels and Bodo[11] have shown that uric acid is destroyed in the liver in dogs; in the present cases the rise in plasma uric acid without a corresponding rise in blood urea, which occurs during the 3 days following the anaesthetic, may be due to diminished uric acid destruction by the liver. The definite fall in plasma uric acid level found 24 hours before any clinical or other biochemical sign of improvement might then be due to a resumption of function by those liver cells which have been damaged but not killed.

The treatment in the present cases differs from that of previously reported cases only in the amount and concentration of the intravenous glucose given. As already stated 50 per cent glucose was given to begin with and the concentration gradually reduced to 5 per cent glucose. The transfusions were given by the continuous drip method and were continued till improvement was established. The favourable results which were obtained, in spite of the fact that 2 of the patients were moribund for more than 24 hours, can probably be ascribed to the early and continued intravenous glucose therapy; they support the view expressed by Sheehan and Townsend that the prognosis in cases

of delayed chloroform poisoning, even with much liver destruction, should not be unduly pessimistic.

I am greatly indebted to Dr. H. L. Sheehan, Director of Research in the Glasgow Royal Maternity Hospital, for encouragement and helpful criticism throughout the course of the work.

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Obituary

Henry Russell Andrews

HENRY RUSSELL ANDREWS, consulting Obstetric Physician to the London Hospital, died on May 7th last, in his home, Iford Manor, Lewes, Sussex, at the age of 71. One of the most popular teachers and sought-after consultants of his day, he was a man who by his sincerity, simplicity, and natural kindness of heart, won in a remarkable degree the enduring affection of his fellow-man.

He was a son of the Rev. John Andrews, vicar of Highgate, whose father farmed his own land in Essex and whose forbears were mostly squires who owned land between the Crouch and the Blackwater. There seem to have been no other parsons or doctors in the family except a cousin who was the doctor at Dunmow, and another cousin who joined the professional ranks by marrying the Rev. W. D. MacLaglan, afterwards Bishop of Lichfield and Archbishop of York.

His mother was the daughter of the Rev. J. E. Nash and Mary Symonds. The Symonds were a distinguished professional family. His mother's father was John Addington Symonds, the well-known Bristol physician and author of several volumes of essays and lectures. Her brother was John Addington Symonds, author, poet and scholar. One of her sisters was Lady Strachey, mother of the first Lord Strachey and of St. Loe Strachey of the *Spectator*, and another sister married Thomas Hill Green, the idealist philosopher and professor of moral philosophy at Oxford University (and the 'Mr. Gray' of 'Robert Ellesmere'). A man often holds the mirror up to his forbears, and Russell Andrews certainly reflected the squire-professional type.

Russell Andrews was one of a family of eight, six boys and two girls. All the others spent a great part of their lives in the Dominions or Colonies. His eldest brother was Director of Education for Western Australia and Pro-Chancellor of the University. One brother went to Canada and thence to the Boer War in Strachcona's Horse, and one joined the Cape Mounted Police and also served in the Boer War. Later on this one and another started

HENRY RUSSELL ANDREWS

farming together in Australia, but joined up at once when the Great War began; the one being killed in the Dardanelles, and the other in France. The remaining brother, a parson, was master at Merchant Taylor's School, and thence went to Central Africa in the Universities' Mission. He was captured by the Germans and held prisoner during the war, but now has a benefice in England. The elder sister also was a teacher in the Universities' Mission; she too was held prisoner by the Germans, and died later in Central Africa. The younger sister has just retired after 24 years as Warden of St. Anne's Diocesan College, Natal, having by her activities added much to its reputation and the number of its pupils. It would surely be difficult to find a more noble family record of service to the Empire than this.

Andrews went to Merchant Taylor's School, matriculated in due course in the University of London, and in October 1889 entered as a student in the London Hospital Medical College, being *proxime accessit* for the Buxton Scholarship in Arts. His chief teachers in clinical subjects were Percy Kidd, Frederick Treves, and George Ernest Herman, who was perhaps the most outstanding teacher of Obstetrics of his day and a great character. As a student Andrews seems to have been a steady worker who passed his examinations successfully, obtaining the M.B. London and the Conjoint Board Diploma in 1894; while at play he is said to have been a hard-working forward in the Rugby football team, Two years at least were spent in holding resident appointments—House Physician, House Surgeon, and Resident Accoucheur in which last he again came under the influence of Dr. Herman, his chief. At the end of this period he took the M.D. London, and went some voyages in the P. & O. Line as ship's doctor, successfully getting rid of the asthmatic attacks that had troubled him since childhood. After this he took the M.D. (London), the M.R.C.P. (London), and was elected F.R.C.P. in 1913.

Having definitely chosen Obstetrics and Gynaecology as his career he was in 1899 appointed Obstetric Registrar and Tutor to the London Hospital and Medical School, holding the appointment for the usual three years. In those days these appointments, of which there was one in each of the three great branches—Medicine, Surgery, and Obstetrics—at all the medical school hospitals, were recognized to be the first step for the aspirant to the coveted membership of the Honorary staff. The appointments were non-resident, part-time and wretchedly paid and, in a big hospital like the " London," were overworked. The holders were cast into the purlieus of Harley Street, and had to make ends meet

by doing odd jobs in their spare time—a few private patients from student friends in general practice, occasional anaesthetics, assisting the Chief operating, coaching and being always on the "cab rank" (in modern parlance the telephone). Nowadays our first assistants are resident, whole-time and have a living wage, with nothing to distract the harmonius gathering of knowledge and prosecution of research. At the end of this appointment Andrews followed the good custom of his day and visited Germany and Austria, then world leaders in academic medicine and research, studying in Berlin and Vienna with Professors Olshausen, Schuata, and others. Soon after his return in 1903 he had the well-deserved fortune to be elected assistant Obstetric Physician to the London Hospital on the unexpected retirement of Dr. Herman. His chief was Dr. Henry Lewers on whose retirement in 1912 Andrews became Senior Obstetric Physician, with Drummond Maxwell as his junior. On the early death of Maxwell in 1915 Eardley Holland became his junior, Gordon Luker becoming co-junior in 1919, and, some years later, Victor Lack was appointed.

In 1926 Andrews retired altogether from the practice of his profession and took a delightful Sussex manor-house near Lewes where he lived for the rest of his life. These, we know, were very happy years for himself and his wife who, by upbringing as well as inclination, shared his zest for social work and politics, sport and gardening, and those other activities that make the full content of a well-lived country life. It was an early retirement, for he was only 55 years old. To be able to retire while still on the high tide of success, before performance has begun to lag behind prestige and the capacity to enjoy physical pursuits has begun to wane, is the good fortune of very few professional men. It must have been a wrench to leave his beloved London Hospital, but all his life he had longed for freedom and the open country. It had been a hard life; the early slavery at the teeming London Hospital, the extra stress of the Great War, when his colleague Drummond Maxwell died and his more junior colleagues were away and he had had to work almost unaided, and the bondage of a big consulting practice. And then there had been that bad illness in 1915—an acute middle-ear infection, followed later by a radical mastoid operation, which left him with double vision for six months and permanently hard of hearing on the affected side—which must have taken toll of his great natural resources more than others or even himself had thought.

It was as a clinician and teacher that Andrews stood out and will long be remembered by students and doctors. His remarkable

judgment was due to a combination of natural gifts with exceptional experience. The foundation of the latter was laid during his years as a junior in the wards, out-patients' department and maternity district of the London Hospital. Few outsiders know what a wealth of clinical material there was in those days, drawn not only from the East End but also from the populous country areas lying north and east, before public assistance institutions had been appropriated by the London County Council, and local hospitals had sprung up in growing towns like Southend. To make the best of these opportunities Andrews brought his natural endowments of mental and physical sturdiness, ability to work quickly, retentive memory, imperturbability, common sense and freedom from doubting that saps the self-confidence of less gifted men. People with these qualities and that experience reach their decisions by a sort of cultivated instinct, rather than by processes of reasoning. Much of his success as a consultant was due to the trust that the medical and lay public had in his integrity and sincerity, and his very presence in anxious and difficult situations brought calm and confidence. He must have saved a remarkable number of women from having unnecessary operations.

As an operator Andrews was in the front rank. His technique was simple and he had the deftness of his former chief, Frederick Treves. In consequence he worked quickly—which was just as well considering the long lists of operations that were piled up for him at the London Hospital. He stuck to his repertoire, and in later years it is doubtful if he added much, if anything, to it. This may have had disadvantages as well as advantages; but, looking back over the last twenty years, there is no doubt that his patients gained far more by his wise conservatism than they lost.

His clinical teaching of students was a pleasure to watch. He enjoyed it, they enjoyed it and, so considerate and kind was he that he made the patients enjoy it too. It was concrete and realistic, emphasising precepts rather than concepts, descriptions rather than explanations. His afternoon teaching clinic, popularly known as the matinee, was always packed. He had a delightful sense of humour, used with courtesy and never at the expense of persons, and always succeeded in enlivening as well as enlightening his audience.

Andrews did his full share of committee and other public work. He was for many years on the Council of the Obstetrical section of the Royal Society of Medicine and in 1924 was its President. In 1925 he was President of the fifth congress of British Obstetrics and Gynaecology. In the foundation of the Royal

College of Obstetricians and Gynaecologists he played a prominent part being a member of the first committee (the other members being Blair Bell, Comyns Berkeley, Ewen Maclean and Fletcher Shaw) formed for the purpose of considering whether the proposals were practicable. When the college was founded he became a member of the first council, was Vice President from 1933 to 1936, and for many years was Chairman of the Examination Committee. He was at various times an examiner in the Universities of Oxford, Cambridge, London and Durham, and for the Conjoint Board, Society of Apothecaries and Central Midwives' Board.

A life so full did not leave much time for writing; but what he wrote was, like his other activities, reliable and thorough, and none the less useful and acceptable for containing little that might be called original work. In 1902 appeared his first published paper, in collaboration with his chief, Dr. G. E. Herman, *A Contribution to the Natural History of Dysmenorrhoea*, being a study of a large series of cases with their clinical correlations and the effect of treatment by cervical dilatation. In 1903 appeared a paper on some work done in the laboratory of Professor Schauta in Vienna, *On the Anatomy of the Pregnant Tube*, demonstrating that the site of embedding was in the muscle and outside the lumen. In the same year appeared his well-known paper, in collaboration with Dr. Cecil Wall *On Chorea in Pregnancy*, based on 40 cases treated at the London Hospital, with a convincing plea for conservatism. He was evidently known as an assiduous reader of foreign journals and a willing worker, for in the space of five years, written "at the suggestion of the editors" (who then were the late Dr. Cullingworth and Dr. J. S. Fairbairn), appeared in the *Journal of Obstetrics and Gynaecology* four of those laborious works, so useful to fellow workers, known as Critical Reviews, on *The Aetiology of Tubal Pregnancy*, *The Internal Secretion of the Ovary* (Ludwig Franckels' exciting paper *Die Funktion des Corpus Luteums* had appeared the year before), *On the effect of Ventral Fixation of the Uterus on subsequent Pregnancy and Labour based on an Analyses of 395 cases* and *Recent Work on Tubal Pregnancy*, each with its long list of references to papers, mostly by German authors. He also published papers on the retraction ring, foetal postmaturity, retroflexion of the uterus, and a Hunterian oration on *The Work of William Hunter in Midwifery*, as well as numerous reports of interesting and unusual cases. In 1906 appeared his widely used little book *Midwifery for Nurses*, the eighth edition of which appeared in 1938. He also assisted in

editing *Midwifery and Diseases of Women* by "Ten Teachers."

An account of Russell Andrews would not be complete without reference to his love of the country and of country sports. One might even say that he was by breed and instinct a countryman fated to live, work and succeed as a townsman. When one caught sight of him in the streets his appearance—big, broad-shouldered, fair and with the ruddy glow of health in his face—was much more that of a countryman fresh from his fields and woods than of a distinguished doctor fresh from the operating theatre or consulting room. His favourite recreations were hunting, fishing and shooting. For many years he hunted from London with the Hertfordshire hounds, stabling his horses at Harpenden, and, after he retired, with the Southdown pack in Sussex He "stalked" chiefly in Sutherland and Ross, and his favourite salmon rivers were the Helmsdale, Borgie and Spey.

In 1914 he married Margaret Dorothea Reynolds of St. Albans, and this resulted in a wonderful companionship. His friends were hers and hers his, and they shared with equal zest the same tastes and hobbies, above all those of the countryside. The sympathy of their many friends goes out to her in her grievous loss.

EARDLEY HOLLAND

I FIRST met Henry Russell Andrews more than 40 years ago when we were both regular attendants at the meetings of the Obstetrical Society of London, long since merged in the Royal Society of Medicine. A popular feature of those meetings was the presentation of specimens from the operation theatre or the "dead-house," and the communication of short clinical records of cases.

It is for many reasons unfortunate that this type of work has fallen into disfavour; it had distinct educational value and it offered to junior Fellows of the Society useful opportunities of eliciting the views of their seniors on points of difficulty.

It was here that Andrews made his first successes. He had recently been appointed as Assistant Obstetric Physician to the London Hospital, and on many occasions he was able to present to the Society pathological specimens of special interest and rare clinical cases; from the cosmopolitan population of the East End an amazing number and variety of such cases appeared to flow into the London Hospital, and Andrews expounded them with enthusiasm. His demonstrations were short, forthright and emphatic, quickly spoken and betraying no sign of the trepidation

from which most of his contemporaries suffered more or less acutely when addressing the obstetric fathers.

The wealth of clinical material which passed through his hands was no doubt an important factor in developing his natural bent for the concrete and the practical, for the study of the plain features of disease rather than for enquiry into causes and origins. It is not surprising that he became a clinical exponent *par excellence* of his subject. He possessed a good memory, retentive in particular of detail, and he was able to draw from his wide experience those personal illustrations and instances which are so valuable in the equipment of the successful clinical teacher.

His "Chief" at the London Hospital, the late Dr. G. E. Herman, no doubt exerted a powerful influence on Andrews during the many years of their association, which extended from his entrance as a first-year student to the time of his Chief's retirement. Herman was a clinical teacher of outstanding force, with a very wide practical knowledge of midwifery. His short text book on "Difficult Labour" was widely recognized as a classic exposition of the English midwifery of his day. To the practical mind of Andrews, Herman must have shone as a guiding star which he could follow unquestioningly. He never deviated from his set course, and became an admirable example of the man who, with a complete knowledge of his field of work, did everything well, and to whom nothing seemed to come amiss. Unlike so many men of his type he never felt the urge to compile series of cases, or to narrate *in extenso* those which had impressed themselves particularly on his memory. Nor had he the gift of the wide outlook which leads men to generalize from particular instances to rules of management. Beyond a short text book for midwives which achieved a wide popularity, he did not leave any sustained literary effort. Although an easy and emphatic speaker, he lacked the fluent pen without which the written narrative often fails to hold the interest of the reader. His work was for his own day and generation.

Success in practice flowed naturally from his qualities, and actually he retired at an early age before his term as Senior Obstetric Physician had expired. He felt little regret at giving up his work in London. A man of powerful physique and abundant vitality, country pursuits always had for him a strong attraction. He rode to hounds regularly for some years before retiring, and it was in the hunting field that he met the lady who became his wife. He was also a keen and successful fisherman. In his small Sussex estate he led the life of a country gentleman with the same

enthusiasm and enjoyment that carried him through his work as an obstetrician, and until the onset of a crippling illness he remained the happy warrior of his early days. Beloved of many friends for his geniality, integrity and loyalty, we bid him an affectionate farewell.

T. W. EDEN

HAVING been asked to write a short appreciation of my late dear friend Henry Russell Andrews memory takes me back to the year 1889 when we both entered the London Hospital as medical students.

A friendship then formed has been uninterrupted until some two years ago, when the symptoms of the slowly progressive and deadly Parkinson syndrome claimed him as a victim.

After qualification our ways diversified as he chose the gynaecological path and I the surgical one. We were both fortunate in becoming colleagues on the London Hospital staff and after 25 years service we both retired, as consultants to the hospital in the same year viz. 1927. I leave others to appraise his active professional ability, but I know the reputation he earned as a most wise and sound gynaecologist and obstetrician. He was a man of the highest ideals, a loyal and trusted friend.

As he enjoyed his work so he revelled in his leisure. In our early years we spent our holidays together on the Continent. Later, when both of us were happily married, our friendship was unimpaired.

I have heard him playfully described as a typical "caveman." If this was an apt description his wife was his true counterpart as hunting, salmon fishing and deer stalking were their special delights.

He leaves behind him an affectionate memory shared by many old friends.

H. M. RIGBY

DICKEY ANDREWS, as he was affectionately known to several generations of London Hospital students, as also to his professional colleagues, was occasionally referred to as the John Bull of Obstetrics. Of fine physique, outspoken, fearing none, he was always just in his estimation of others, never a back-biter, ready to give credit where it was due and ever willing to assist, so far as he was able, his students and professional brethren. Straight as a die, beloved by his patients, very sane, unselfish, a wise counsellor and imbued with a fine judgment, he was an outstand-

ing personality in that department of medicine in which he practised. If he did not make friends so easily as some, nevertheless those of us who could claim his friendship had always a tower of strength upon which to lean in any difficulty, either professional or in the more intimate aspects of private life; his kindly greeting and helping hand will always be remembered. The interests of his hospital patients were paramount, to all of whom he extended cheerfulness, kindness and courtesy.

Retiring from active practise earlier than most men, and so personally unknown to the younger generation of obstetricians and gynaecologists, Russell Andrews, living in an attractive Manor House in Sussex, took a keen interest in local affairs and otherwise spent most of his spare time in gardening, fishing, hunting and shooting. He was essentially a sportsman in the best sense of the term and although he did not take up such pursuits actively till middle life, he applied to them the same care, concentration and study as he had done to his professional work and with a similar success.

Russell Andrews was a Director of this Journal from 1921, and from 1919 till three years ago he read the galley proofs of every article published. Being well read and having considerable literary ability, including a knowledge of French and German, the great assistance he rendered to the Editor in these respects is remembered with especial gratitude.

Andrews was never so happy as when, accompanied by his wife, they were engaged in hunting, salmon fishing, covert shooting or deer stalking, and the sincerest sympathy of his many friends goes out to her in her loss. Few women have had greater happinesss in their married life than she had. He was a great gentleman.

COMYNS BERKELEY

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

The Quarterly Meeting of the Council was held in the College House on Saturday, 25th July, 1942, with the President, Sir William Fletcher Shaw, in the Chair.

Sir William Fletcher Shaw, M.D., Ch.B., F.R.C.P., F.R.C.O.G., F.A.C.S. (Hon.), was re-elected President to take office in October, next.

The following officers were also elected:

Vice-Presidents:

William Gough, M.B., B.S., F.R.C.S., F.R.C.O.G.
Charles Gibson Lowry, M.D., F.R.C.S.I., F.R.C.O.G.

Honorary Treasurer:

John Prescott Hedley, M.A., M.B., *M.C.*, F.R.C.P., F.R.C.S., F.R.C.O.G.

Honorary Secretary:

George Frederick Gibberd, M.B., M.S., F.R.C.S., F.R.C.O.G.

Honorary Librarian:

Wing Commander Frederick Roques, M.A., M.D., M.Ch., F.R.C.S. F.R.C.O.G, (R.A.F.V.R.).

Honorary Curator of Museum:

Aleck William Bourne, M.A., M.B., Ch.B., F.R.C.S., F.R.C.O.G.

The following candidates were elected to the Membership:

Herbert Agar, R.A.M.C.
Muriel Boycott, London.
John Wilfred Douglas Buttery, Folkstone.
Marie Hall Calverley, Northampton.
Thomas Ayton Gillie, Dumfermline.
Ian MacGilchrist Jackson, London.
Walter Johnston McCord, Sheffield.
Mary Kathleen Lawlor, Gold Coast Colony, West Africa.
Herbert Marx Wolff, Pennsylvania.
John Forrester Brown Wyper, Aberdeen.

The following was admitted in absentia to the Fellowship of the College:

Leslie Cecil Lloyd Averill, New Zealand.

BOOK REVIEWS

" Diseases of Women." By HARRY STURGEON CROSSEN, M.D., F.A.C.S. and ROBERT JAMES CROSSEN, A.B., M.D. Published by Henry Kimpton, 26 Bloomsbury Way, W.C.1. Price 63s. net.

IN this edition the authors have carried out a complete revision and the illustrations, with the addition of 145 new plates, now reach the imposing total figure of 1127 with many in colour. The general result is a very complete and up-to-date compendium of modern gynaecology. The subject matter follows the usual anatomical arrangement and in general it is handled with the mastery to be expected from authors with such wide experience. The first chapter (100 pages) on Anatomy and Physiology is excellent. The second chapter (114 pages) on Gynaecologic Examination and Diagnosis, while competent and practical, is spoiled to a certain extent by a somewhat excessive array of rather poor photographs. For some reason, also, which is not clear 4 good drawings from Kelly's Operative Gynecology exhibiting different kinds of abdominal swelling appear in their original form and have been redrawn in simpler line to form 4 additional illustrations, all 8 figures appearing within a few pages. In this chapter one page only is devoted to Backache, which in a book of 920 pages seems rather scant treatment of such an important subject. There is no reference at all to one of the most important causes of gynaecological backache, namely that dating from pregnancy and childbirth, and there is little attempt to guide the student in the difficult matter of differentiating the various types of backache so commonly met with. The remaining chapters (III to XIII) which deal with Gynaecologic Treatment Measures and the systematic discussion of the diseases of the various organs and regions are of a high standard. In other chapters Sterility and Sexual Disturbances and the Lower Intestinal Tract in Relation to Gynecology are well handled. We find the chapter on Menstrual Disturbances the only poor section of the book. It is restless and disjointed and is not calculated to help a doctor faced with a personal problem of diagnosis and treatment. Thus in discussing menorrhagia and metrorrhagia in the Developmental Period (10 to 20) it is stated that the " order of treatment . . . will be about as follows ": (1) Regulation of diet. (2) Thyroid therapy when the basal metabolism indicates a need for it. (3) Ergotrate in atonic individuals. (4) Snake Venom. (5) Hormone Therapy—here there is a long uncritical statement of the various hormonal possibilities. (6) Curettage. (7) Radiation, (8) Operation. In the difficult and fluid state of hormonal therapy we may assume that one of the main functions of a

standard textbook should be to sort out for the reader as far as possible the proved and established data from that which is unproved and speculative. A statement based upon the record of a few cases by a single writer should not usually find place in such a textbook. In this respect we find the present chapter unsatisfactory. Thus on the evidence of one published article snake venom is given a prominent place in the management of a case of uterine bleeding. In another connexion, reference to the use of pregnancy urine for dysmenorrhoea, it is stated that " in an article last year Novak advised giving 200-500 U. daily for a week before the period." We find many such unsubstantial and airy injunctions scattered throughout this and other sections. Finally the book does not detail the operative procedures. For this aspect of the subject the reader is referred to the authors' well known book on Operative Gynecology.

JAMES YOUNG.

" Diagnosis and Treatment of Menstrual Disorders and Sterility." By CHARLES MAZER, M.D., F.A.C.S. and S. LEON ISRAEL, M.D., F.A.C.S. With 108 illustrations. Published by Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price $ 6.50.

THIS volume is an excellent sample of the type of medical literature which America has made peculiarly her own. Its format is massive, even sumptuous, its illustrations are numerous and appropriate, it is comprehensive and scholarly, it is well documented from the experience of the authors and from the literature and each chapter has its bibliographical appendix. Dealing with a subject, which is in a state of constant flux, it is more a compilation or monograph than a textbook. The first four chapters are devoted to sex physiology, the following chapters dealing symptomatically with the menstrual disorders (dysmenorrhoea, amenorrhoea, hypomenorrhoea, uterine bleeding) and there are interesting chapters devoted to Premenstrual Tension, Migraine, Breast Hyperplasia, Intermenstrual Pain and Vicarious Menstruation. The final section—more than a quarter of the volume—is devoted to sterility.

Throughout, we find the handling of the material to reach a high average standard. The outlook is fresh and enterprising and, on the whole, judicial. Where a main aim has been the comprehensive presentation of work, much of which is recent, a rigidly critical attitude could hardly have been expected. In many instances it is clear that new work is presented more on the authority of the original investigator than on the conviction of the co-authors of the book. We have found some few statements in which our experience is at variance with that of the authors. Thus on pages 61 and 62 they state that the " withdrawal of intensive estrogen treatment in menopausal women who have not menstruated for several years is infrequently followed by uterine bleeding." We find such withdrawal bleeding very frequent even in aged women with stilboestrol. Again on

page 134 they refer to "intra-abdominal haemorrhage arising from a ruptured graafiian follicle or corpus luteum—a condition recently described by Hoyt and Meigs, Israel and others." This condition has been well known to gynaecologists and in the literature for very many years. In discussing Pituitary Cachexia (Simmonds' Disease) on page 165 there is no reference to the work of Sheehan on the correlation between puerperal haemorrhage and pituitary necrosis.

JAMES YOUNG.

"A Handbook of Midwifery for Obstetric Dressers, Pupil-Midwives and Midwives." By SIR COMYNS BERKELEY, M.A., M.D., M.C., F.R.C.P., F.R.C.S., F.R.C.O.G., M.M.S.A. (Hon.). Published by Cassell & Co. Ltd. Price 8*s*. 6*d*.

THE phenomenal success of this Handbook of Midwifery (a new edition is now called for every three years, and 62 thousand copies in all have been printed) is worth investigating.

A careful perusal of it convinces an experienced reader of the pains which have been taken to make its facts and explanations not only readily understood but also easily memorized.

Many of its pages bear evidence of the author's deep concern not only directly to promote the welfare of expectant mothers and their babies, but also indirectly, by improving pupil midwives' chances of passing the C.M.B. Examination with distinction. During her future career the midwife should keep this book for ready reference, and be determined to consult each new edition in order to keep her knowledge up to date. The teaching throughout embraces sound midwifery practice without lapsing into controversial problems. The author is surely right in retaining the short accounts of medical treatment, which have been criticized. It is well for midwives to be prepared mentally for the doctor's line of action, just as it is advisable for the obstetric dresser to know how much is taught to midwives.

In the Preface the author significantly states that he gladly avails himself of reviewers' suggestions. One therefore feels it a duty to submit two or three points for his consideration. He refers to the pain and scratches occasionally inflicted on the abdominal skin of patients at C.M.B. practical examinations, by the "fang-like nails," which he even likens to those of "harpies," of some of the candidates. Would it not be better to omit the word grasp (grip is even worse) in teaching the art of abdominal palpation. "Light intermitting touch" gains much more information. Then, again, the lower pole, as Pinard first taught, should be investigated first, and not last, for several good reasons. The author himself points out that superior palpation is apt to excite uterine contractions. Manual pressure to assist delivery of the aftercoming head must be suprapubic, not fundal; the latter is likely to cause premature and harmful separation of the placenta: indeed the artist appears to have known this (see figs 69 and 73).

The general recognition of the success of sulphonamide treatment of

ophthalmia neonatorum was, no doubt, just too late to justify inclusion.

In an appendix there are three concise essays on (1) food, (2) bacteriology and (3) blood transfusion. The table of vitamins could be made more explicit.

The book is of convenient size, admirably printed, generously illustrated and provided with a most helpful index.

M. H.P.

"Pédiatric Gynaecology," SCHAUFFLER.

A MEDIUM-SIZED volume of 357 pages, devoted to the consideration of the genital organs (250 pages) and to a lesser extent the other pelvic viscera (100 pages) in female children up to and including the age of puberty.

The author, the assistant clinical professor in the University of Oregon Medical School, has developed his present teaching and practise from experience derived in a special juvenile gynaecological clinic during the last 15 years, together with an extensive study of the literature relating to gynaecology in this age period. There is marked stressing of the importance of correct psychological approach, which may seem rather excessive and irritating to the British reader.

Clinical examination of children is very clearly described, and then a regional consideration of the genital tract from below upwards is given, chiefly clinical but including necessary facts embryological, anatomical and physiological.

The consideration of the urinary and lower alimentary tracts is much wider than differential diagnosis requires and includes much usually regarded as outside the province of the gynaecologist in this country.

Finally social service, and medico-legal related problems are reviewed but here again refer to those of America.

A valuable occasional reference book for those practising gynaecology or in charge of child-welfare clinics. Treatments are essentially up to date, but local treatments to the infantile genital tract are certainly undertaken much less commonly in this country without much subsequent evidence of harm from their relative neglect. The whole style, presentation and subject matter is far more suitable for postgraduate than undergraduate consideration.

ALAN BREWS.

Review of Current Literature

Director: FREDERICK ROQUES, M.A., M.D., M.Chir. (Cantab.), F.R.C.S., F.R.C.O.G.

THIS Review contains the lists of contents and abstracts of the more important articles from the journals with which the *Journal of Obstetrics and Gynaecology of the British Empire* exchanges.

The Review of Current Literature has kept the readers of the Journal in touch with current literature throughout the world; owing to the war many journals with which the *Journal of Obstetrics and Gynaecology* previously exchanged are no longer received. At the end of the year an Index of all the subjects contained in the articles of the journals reviewed is printed. Arrangements are also made to include abstracts of important articles on border-line subjects, such as Physiology, Biology, and Biochemistry.

LIST OF ABSTRACTORS

J. LYLE CAMERON, F.R.C.S.; W. E. CROWTHER, M.B.; R. H. B. ADAMSON, M.D.; B. JEAFFRESON, F.R.C.S.; P. MALPAS, F.R.C.S.; T. N. A. JEFFCOATE, F.R.C.S.; MEAVE KENNY, F.R.C.S.; JANE H. FILSHILL.

The Canadian Medical Association Journal

Vol. xlv, December 1941, No. 6.

*The management of carcinoma of the cervix uteri. B. R. Mooney.

*Foetal shock, treatment with desoxycorticosterone acetate. Melvyn Berlind.

*Local anaesthesia in obstetrics. N. W. Philpott.

*The use of vitamin P in the oedema of pregnancy toxaemia. Evan Shute.

THE MANAGEMENT OF CARCINOMA OF THE CERVIX UTERI.

A group of 115 patients treated in the three-year period between November 10th, 1937, and November 10th, 1940, is discussed. They were considered under the headings *Diagnosis* and *Treatment*. Reports on the follow-up of these cases were not made. The X-rays employed in the treatment were produced by a 400 kv. machine. Daily records were kept of the dosage, and of the condition of the patient while under treatment. Notes included complete blood-counts made weekly, cell-volume, icterus-index and sedimentation-rate, and the findings resulting from frequent pelvic examination.

In the Province of Manitoba under the Cancer Relief and Research

Institutes it was found that radium treatment was adequate, but X-ray equipment would, as a result of this investigation, need to be doubled. The registered death-rate from cancer was mounting until the year 1939, when it was shown to hold second place among the five leading causes of death. These statistics were equally applicable to cancer of the cervix. These causes of death for every 100,000 of the population of Manitoba in 1939 were as follows: Cardiac cases 146, cancer 118.9, tuberculosis 50.5, accidents 45.2, pneumonia 34.1.

The diagnosis was usually obvious in the majority of cases, but was always verified by biopsy, which furthermore permitted histological grading. The cases were graded clinically and pathologically. Clinical grading was as follows: stage 1, primary lesions limited to the cervix; stage 2, primary lesions in the cervix with moderate extension into the parametrium or vaginal wall, uterus freely movable; stage 3, primary lesion extending well into the parametrium with fixation of the uterus; and stage 4, advanced disease with fixation of the uterus or distant metastases. The pathological classification was made into 3 grades. Grade 1, adult type, made up of highly differentiated cells with a tendency to cornification and formation of pearls, radio-resistant. Grade 2, a plexiform type, in which the cells have lost most of their squamous character, show a plexiform arrangement, a tendency to infiltration and a moderate degree of anaplasia, more radio-sensitive. Grade 3, the anaplastic type, in which the cells have lost all squamous character and are completely undifferentiated and diffusely invasive, highly radio-sensitive. Of the author's series, 13 per cent were in stage 1; 37 per cent in stage 2, 47 per cent in stage 3, and 5 per cent in stage 4. According to pathological grading 4½ per cent fell into grade 1; 45 per cent into grade 2; and 50 per cent into grade 3.

Experience seems to teach that radiation treatment is more effective in grades 2 and 3, while surgical results are better in grade 1. The author is of the opinion that the clinical stage of the disease is much more important than the histological grade.

Early diagnosis is, however, of the greatest importance. Abnormal vaginal bleeding is the most common and also the earliest warning. The slightest amount of irregular bleeding, or of blood-stained discharge, must be regarded with suspicion, and demands immediate and thorough investigation, which should include biopsy of the cervix, if there is the slightest reason to suspect the presence of cancer. All abnormal discharges from the vagina should merit investigation. It was frequently stated by patients that they delayed investigation because of the expense it might entail.

Before treatment was started, a full investigation was made of the patient's general condition, and when the patient was found to be debilitated by haemorrhage and infection, a course of treatment was given by transfusion and other medical measures. The prognosis in cases of elderly women with degenerative disease, and in the young, was not good. Further considerations were given to the clinical stage of the growth, to the presence or absence of pyogenic infection, the histological grade, and to the type of

growth, whether fungating or ulcerating. Regard must be had for the patient's economic status. Every care must be taken to avoid inadequate and ineffective treatment once it is instituted; the first attack is the important one.

Foremost endeavour must be made to prevent the spread of cancer, locally and by metastases, and care must be taken to control if possible pyogenic infection, especially sepsis of the urinary track.

Treatment was planned according to the clinical stages. There were three methods by which this could be effected—treatment with radium, X-ray radiation and by surgery.

In clinical stage 1, only radium was most commonly used; but if there were any suspicion that the disease had gone beyond the cervix, a complete course of X-rays was given. It was not possible for the author to employ an intravaginal cone placed in contact with the growth; but he considered this the proper way of using it.

In the series of cases not considered, only four were treated by operation, and of these four cases, all had previously been treated by operations on the cervix, such as repair or amputation.

Cases in stage 2 were, after careful consideration, treated first with X-rays, afterwards with radium. The method had the advantage that infection could be cleared up during the X-ray treatment, fungating growth could be destroyed and the cervical canal could thereby be more easily found and dilated, and there would be little likelihood of metastatic spread of the growth during dilatation. On the other hand, serious results were likely to follow the placing of radium into an already infected cervix, thereby producing a slough which would augment infection. Cases in stage 3 were considered and treated as those in stage 2. In cases classified in stage 4, it was considered that the treatment was almost entirely palliative, but it was surprising to find that there were a few five-year survivals as a result of this treatment. Satisfactory treatment could only be given when adequate machinery is available, when trained radio-therapists are in attendance, when the patients are kept closely under observation, and when the dosage is adjusted to suit the patient.

Complications of the treatment as noted by the author were: asthenia, diarrhoea, nausea, vomiting, frequency of micturition and skin affections. Seldom, however, were these conditions so serious as to necessitate the interruption of the treatment. Usually the more serious symptoms were noted when employing the 400 kv. as compared with the 200 kv. machine. The latter, however, seemed to produce nausea and skin affection more frequently. Blood investigation did not show that there were any blood changes attendant upon X-ray therapy. Diarrhoea seemed to be troublesome when full doses of radiation were given and more especially if this was combined with radium treatment. Again, this symptom seldom demanded a suspension of the treatment. Usually it was found that symptoms were less distressing when X-rays and radium were not employed at the same time.

Of the cases seen it was shown that permeation was present in 65 per

cent; metastases in 9 per cent; recurrence and metastases in 4 per cent; recurrence in 8.5 per cent; permeation and metastases in 8.5 per cent; and permeation and recurrence in 5 per cent.

A series of highly explanatory charts are included in the text, and a full bibliography is provided.

FOETAL SHOCK, TREATMENT WITH DESOXYCORTICOSTERONE ACETATE.

Numerous writers have borne testimony to the belief that there is some relation between adrenal insufficiency and shock. Scudder, in his book on this subject, gives a bibliography of 533 references. Vast numbers of experiments have been made on dogs, guinea-pigs, rats, and mice. These experiments showed that the administration of histamine was followed by a state of shock, but the previous administration of large doses of normal saline enabled rats to withstand twice the lethal dose of histamine for normal animals. Shock associated with intestinal obstruction in dogs was greatly mitigated by treatment with adrenal cortical hormone. This hormone is now prepared synthetically and used under the name desoxycorticosterone acetate. It has been reported that Addison's disease in human beings has been treated by this substance with good results. Some unfavourable responses to indiscriminate and excessive use of this synthetic product have also been reported. Some of the results mentioned have been the production of marked oedema, high tension, and congestive heart failure. Atrophy of the normal adrenal cortex may follow excessive dosage in normal animals and a warning note against the risks attending indiscriminate use of this substance has been sounded.

Kendall and others have shown that there are qualitative as well as quantitative differences in the preparations derived from adrenal cortex, and that in the treatment of Addison's syndrome desoxycorticosterone is not a complete substitute for the adrenal cortex. It was with caution, therefore, that the author undertook to study the effects of desoxycorticosterone in infants suffering from foetal shock, a condition characterized by extreme flaccidity of all the muscles, feeble and irregular cardiac action, pale colour and weak, gasping respirations in the newborn. This condition is usually attended by low blood-pressure of 40, 30 or even 0 mms. instead of the average reading of 50 to 60 mms.

A very full report is given of the treatment in 12 cases of foetal shock by means of normal saline plus desoxycorticosterone injected in doses of 0.5 c.c., down to 1 c.c. of the substance as an initial dose, followed up by 0.25 down to 0.1 to 0.2 c.c. daily for 10 days; 100 c.c. of normal saline was given hypodermically to eight of the cases. In the majority of these babies the results appear to have been extremely good; cases in which profound shock was noted at birth have, after 24 hours, shown an amazing improvement and a healthy appearance. The author is of the opinion that in a parallel group of patients deprived of the benefits of desoxycorticosterone acetate, some of the babies would have died.

A chart giving a full and detailed report of these cases is included, and a very extensive bibliography.

LOCAL ANAESTHESIA IN OBSTETRICS.

Child-bearing is a painful ordeal, probably becoming ever more difficult. While the relief of pain in childbirth has everything to support it, the first endeavour should be to make childbirth safe for the mother and for the baby. It has been shown that respiratory movements tend to occur regularly in the latter third of uterine life. Gas, however, is not inhaled, but rather amniotic fluid, which is drawn into the lungs and expelled. A baby should breathe within a few seconds of birth, and if it fails to do so, there must be a cause. It has also been shown that brain cells need oxygen and that if they are deprived of it for one minute, they will die. Furthermore it has been demonstrated that certain degenerative changes in the brains of older children are directly traceable to asphyxia at birth. This asphyxia again may be due to excessive administration of sedatives to the mother. Reports on 200 cases of delivery have been made. Half of these received ether, and paraldehyde *per rectum*. The average time for the first breathing was 39.5 seconds. The other half of the cases received no analgesia, and in this group the average time for the first breathing was 8.9 seconds. These facts, viz. that anoxia and asphyxia may be followed by damage to the cerebral cells, should be a warning that the employment of all kinds of anaesthesia may be attended by dangers for the baby.

Cole and Kimball investigated 5,000 deliveries of all kinds. Many of the patients received heavy doses of sedatives such as paraldehyde, morphia, scopolamine, nembutal, ether sodium, pentothal, and others in addition received ether, nitrous oxide and oxygen, cyclopropane and spinal anaesthetics. The results revealed that the chief causes of asphyxia in order of importance were: prematurity, difficult or precipitate labour, dystocia and difficult forceps delivery, sedatives of varying amounts and general anaesthesia.

The author has endeavoured, in view of the facts stated, to control the amount of sedatives and general anaesthesia given and, in all cases, to pursue a middle course.

Local anaesthesia has been used, either alone or with small doses of sedatives such as one twenty-fourth of a grain of heroin. This has been employed in toxic cases, breech cases and Caesarean section. In toxic cases it is most important to avoid excessive bleeding and the risk of puerperal sepsis. Heavy doses of sedatives or prolonged anaesthesia increase these risks. During the second stage of labour light nitrous oxide and oxygen anaesthesia is given, and when the perineum becomes distended, it is freely injected with 1 per cent novocaine plus adrenalin. Block injection is made to involve the pudendal nerves, the sensory branches of the ilio-inguinal and posterior femoral cutaneous nerves. Under this treatment the forceps is almost never necessary and the baby cries freely as soon as it is born. The placenta comes away easily and post-partum haemorrhage seldom occurs. This treatment appears greatly to have reduced the foetal death-rate in toxic cases. Breech cases are treated in a similar manner and when this is carried out there is seldom any difficulty in delivering the after-coming head.

Caesarean section is still attended by a high mortality-rate, both for

mothers and babies. This is especially so in cases of heart disease and tuberculosis. Local anaesthesia has very much to be said in favour of its employment in all cases of Caesarean section, and especially in tuberculous and cardiac cases; there are many advantages for the mother and the child. One of the outstanding benefits is the absence of influence on respiration. The local anaesthetic used was novocaine, 1 per cent with adrenalin 5 mms. to every 150 c.c. of the solution used. The skin was infiltrated, and deep nerve block in three layers was made.

A very short bibliography and *résumé* in French are appended.

THE USE OF VITAMIN P IN THE OEDEMA OF PREGNANCY TOXAEMIA.

It is believed that the oedema associated with the toxaemias of late pregnancy is due in part at least to an increased capillary permeability. Citrin (vitamin P) is said to control this permeability.

A group of 16 pregnant women was chosen. In all oedema was marked. They were given citrin daily in doses varying from 60 to 120 mgm. It became apparent that no effect could be detected. The weight curve was unaffected, as were other signs of toxaemia. A further series of 4 pregnant women with oedema due to late toxaemia was then given 900 mgm. of citrin daily. These also appear to have been unaffected by the administration of this substance.

A very short bibliography and a *résumé* in French are appended.

The Journal of the American Medical Association

Vol. cxvi, No. 26, June 28th, 1941.

*Heparin as a prophylactic against thrombosis. C. Crawford and E. Jorpes.

HEPARIN AS A PROPHYLACTIC AGAINST THROMBOSIS.

Three hundred and twenty-five patients were given heparin after operation. None of them developed any thrombo-embolic complications, as compared with an incidence of such complications in 9 per cent of a control series of 1,111 cases. After 88 gynaecological operations no instance of thrombosis occurred under heparin as compared with a 4 per cent incidence in a control series of 1,054 cases. The heparin used had a strength of about 70 per cent of the pure mucoitin trisulphuric acid. It was given as a 5 per cent solution intravenously four times a day. The dose was 250 to 400 mgm. daily and continued for 5 to 10 days.

The chemical nature of heparin is well established. Being a mucoitin polysulphuric acid with not less than 40 per cent sulphuric acid the heparin polysaccharide possesses a high negative electric charge which enables it to react with some of the components of the coagulation system. Heparin is produced by the mast cells of the connective tissue, situated mainly around the smaller blood-vessels. The metachromatic granules of these cells consist of heparin. The authors recommend the use of large doses until more experience is forthcoming about the minimal effective dose. They gained the impression that heparinization should not be stopped abruptly, fresh emboli being prone to occur within 10 to 15 days of sudden withdrawal of the hormone.

PERCY MALPAS

REPORTS OF SOCIETIES

THE ROYAL ACADEMY OF MEDICINE IN IRELAND

A meeting of the Section of Obstetrics of the Royal Academy of Medicine in Ireland was held in the Royal College of Physicians on Friday, November 14th, 1941; the President, Dr. Ninian Falkiner, was in the Chair.

Dr. R. M. CORBET showed

TWO SPECIMENS OF A UTERINE RUDIMENTARY HORN.

The first specimen contained a foetus which had reached about 16 weeks' development, and which had been dead for six months.

The patient was a multipara who had been married 9 years and had had 5 full-time normal confinements. The vagina and cervix were normal, and the rudimentary horn had attached to it a normal Fallopian tube and ovary, but was itself attached to the uterus by a thin pedicle. There appeared to be no connexion between the horn and the uterine cavity. The patient had menstruated at a 28-day interval, with average menstrual loss for three or four days; menstruation was painless.

The second patient was a multipara, aged 35 years; she had been married for 7 years, and had had 2 full-time children and an abortion in September of this year.

Examination showed a normal vagina and a parous cervix; on bimanual examination, a cystic swelling could be felt lying to the right of the cervix, above the right vaginal fornix and bulging down into it. On the left, above this swelling, was felt the fundus of the uterus which was in direct communication with the vaginal cervix, and, on the right, a hard mobile mass, suggestive of a smaller fundus.

At laparotomy, the mass was found to resemble a small uterine fundus and to terminate below in the cystic swelling already mentioned. It appeared that the right Fallopian tube and ovary had been removed at a previous operation for appendicitis with peritonitis.

The rudimentary horn was removed and the cystic swelling was found to contain menstrual blood. On re-examination from below, the menstrual blood was now found to be draining through the cervix. The opening in the upper part of the sac was closed, and the abdomen was closed without drainage.

This type would appear to lie between a uterus pseudo-didelphys, in which both halves are capable of functioning, and a uterus unicornis cum rudimentarius, in which the horn is often very small indeed.

The collection of menstrual fluid would appear to have been in an expansion of the fine canal which connects the cervix to the rudimentary horn in a number of these cases.

The President said that Dr. Corbet was unusually fortunate in his experience of this type of case. The interest in a rudimentary horn which became

pregnant was both from the specialist side and from the clinical side. Eighty-four of these cases had been reported in the literature, and in the majority of them the horn had been on the right side. In both Dr. Corbet's cases the horn was on the left side. The clinical importance of pregnancy in a rudimentary horn was very great. Dr. Corbet's second case was similar to one which had been shown at the Section by Dr. Davidson some years ago, in which there was a haematocolpos communicating with one horn of the uterus.

Dr. J. S. QUIN said that Dr. Corbet had been lucky in having come across two of these abnormal cases within a year, and so it was easier for him to make the diagnosis before the abdomen had been opened. Dr. Corbet's case was definitely one of uterus didelphys. The question was whether one was dealing with pregnancy in a rudimentary horn or with an ectopic pregnancy. The clinical difficulty of diagnosing an ordinary straight case of retroversion was often very great. A patient who had recently been under his care had been given an anaesthetic and while she was under the anaesthetic he and his colleague were still in doubt regarding the condition with which they were dealing. They decided that it would be safer to open the abdomen and replace the uterus from within. It was then found that the case was one of pregnancy in one horn of a uterus didelphys. The uterus was replaced, the patient carried on to term, and the baby was delivered without any difficulty.

Dr. T. M. HEALY said that he had not had a very large experience of these cases. He had seen three pregnancies in rudimentary horns. He had once removed a recently pregnant horn under the mistaken diagnosis of a fibroid. He had been present at the delivery of a baby in a case of uterus pseudo-didelphys in which the baby had come out of the left horn of the vagina. Later he had operated with a view to removing the left rudimentary horn and had found that the trouble was on the right side.

Dr. CORBET thanked the President and the Section very much for the way in which his communication had been received.

Dr. Healy had called attention to the termination of a pregnancy in a rudimentary horn, by rupture, which was, clinically, the most important and was said to occur in 45 to 47 per cent of cases. Of the remainder, most of them terminated as this one did, in the death and retention of the foetus, while there was on record a number of cases in which the pregnancy had actually gone to term in the rudimentary horn.

With regard to Dr. Quin's case, in which the pregnant horn of the uterus was in retroversion, the presence of the vaginal septum made it impossible to replace the uterus manually, and, of course, even if this had been done, a Smith Hodge pessary could not have been inserted without removing the vaginal septum.

He was glad to hear that Dr. Quin's case had terminated so favourably.

Dr. A. BARRY read a

REPORT OF TWO CASES OF HYDATIDIFORM MOLE.

Case 1. A primigravida, aged 23, was seen after 7 weeks of amenorrhoea: the diagnosis of normal pregnancy was made. Irregular bleeding occurred from the ninth to the fifteenth week, when a diagnosis of mole was confirmed

by the Zondek-Aschheim test in dilution, and by X-rays. Spontaneous evacuation of the uterus after the administration of five doses of stilboestrol of 1 mgr. each, at intervals of an hour. Curettage six weeks later was followed by negative Zondek-Aschheim tests, until a normal pregnancy supervened.

Case 2. A multipara, aged 50, was seen at the eighth week of pregnancy with a history of slight bleeding from a very much enlarged uterus. The diagnosis of hydatidiform mole was confirmed at 10 weeks by the Zondek-Aschheim test in dilution, and by X-rays. The uterus was emptied by medicinal induction. The puerperium was febrile. In one month haemorrhage recurred: curettage now showed the case to be one of chorion-epithelioma: total hysterectomy was performed. The patient was alive and well one year later with negative Hogben test.

The President said that Dr. Barry had given a very clear description of these two cases. It was rather unusual to hear cases of hydatidiform mole described from such an early period of pregnancy and carried on to their termination. The second case was of special interest to him, because the last patient with hydatidiform mole whom he had seen was a woman of over fifty years of age; she was found to have a malignant mole which had turned into a chorion-epithelioma.

Dr. T. M. HEALY said that he had seen the first of these cases. It seemed to him to be in every way a normal pregnancy. His experience of cases of hydatidiform mole after the patient had lost any blood had made him think that the uterus was always tense and never boggy. He was interested to hear that in the second case Dr. Barry considered that the uterus was boggy before the patient had lost any blood. He wondered if this was usually the case.

Dr. R. M. CORBET congratulated Dr. Barry on the successful issue in the cases which he presented, and on the number of interesting points which were raised. In Dublin the incidence of hydatidiform mole was, approximately, 1 in 1,200 cases. He had never seen a case in so old a patient as in Dr. Barry's second case, but he had had two in private practice in patients over 40 years of age. He was quite satisfied that the diagnosis of hydatidiform mole was only tentative until part of the mole was seen; and was impressed by Dr. Barry's remarks on the Zondek-Aschheim reaction.

With regard to the treatment employed; since he had heard Dr. John Cunningham's account of the medicinal induction of these cases, he had used it himself, but, when the mole was in the process of expulsion, he always explored the uterus to make sure that it was really empty. Ten days later, the uterus was lightly curetted, and the curettings were sent for microscopical examination. He thought that the Zondek-Aschheim reaction should be performed monthly, for, at least, six months.

The immediate mortality of a mole appeared to be not more than 1 per cent. The real danger was the subsequent development of chorion-epithelioma, which was calculated to occur in from 6 to 10 per cent of cases; and he thought that the Zondek-Aschheim test, although it was by no means 100 per cent reliable, was a help in the early diagnosis.

Dr. G. C. DOCKERAY referred to a case in which the Zondek-Aschheim test had been positive on two occasions. Nothing of an operative nature was done,

and eventually the test became negative. In cases in which any villi were found it was probable that the condition was not chorion-epithelioma but an intravenous mole. He mentioned a case, which he had recently seen in the Rotunda Hospital, of malignant mole in which there was no evidence of any villi but just masses of mangate cells. It was quite possible in an early case for the curette to miss the chorion-epithelioma. There was, he thought, a slight discrepancy in the teaching as to how often the Zondek-Aschheim test should be done after a mole had been found, and how often it was actually done.

Dr. F. W. DOYLE said that he thought that the uterus should be lightly curetted in these cases, as had been done in the old days. At that time there did not appear to have been any trouble at all from haemorrhage. He wondered if the drugs which were now used so extensively would have any subsequent effect on the endometrium.

Dr. EDWARD SOLOMONS said that in certain cases the Zondek-Aschheim test was distinctly misleading. Dr. Mitchell and he had recently reported a case of chorion-epithelioma in which the test was negative. He asked Dr. Barry on what grounds he considered that stilboestrol was useful for medicinal induction in these cases. He was under the impression that it was of use only in cases in which the foetus was dead.

Dr. BARRY, in replying, said he thought that hysterectomy should have been performed in the second case and that abortion should not have been medically induced. He was of the opinion that the Zondek-Aschheim test should be done for some considerable time after an abortion had occurred. He always used stilboestrol when he was trying to induce abortion.

Dr. N. McI. FALKINER read an account of

A CASE OF FAILED FORCEPS.

The patient, a primigravida, had been admitted to the Rotunda Hospital after twelve hours' labour. The history showed that repeated attempts had been made some three hours before admission. Apparently the forceps had slipped and had been reapplied. On admission to hospital the patient was in fairly good general condition but the vagina, cervix and perineum were lacerated; on vaginal examination the foetal head could be felt in a collapsed condition. Conservative treatment resulted in the delivery of a stillborn child three hours after the patient's admission to hospital. The skull of the infant was fractured, there was a large intracranial haemorrhage. The fracture involved the occipital bone and the parietal bone.

Dr. Falkiner then gave a short account of the dangers of failed forceps cases. He suggested a classification and commented on the dire results following the unjustifiable use of forceps.

Dr. R. M. CORBET entirely agreed with the President's definition of failed forceps and thanked him for bringing down this remarkable exhibit.

During the years 1936 to 1940, 19 cases, which fell within the President's classification, had been admitted to the Coombe Hospital. Three of the patients had died, giving a mortality rate of 15.7 per cent. In addition, 4 cases were morbid, giving a total mortality rate of 36.8 per cent. There were

11 dead infants, giving a gross infant mortality rate of almost 58 per cent. In no case in which forceps delivery had been attempted had the conditions been fulfilled, and the findings at examination on admission included 4 brow presentations, disproportion, hydrocephalus, and compound presentations. Four cases terminated in craniotomy, 2 in lower segment Caesarean section, 2 in Caesarean hysterectomy, and the remainder were delivered vaginally, by various means, without reducing the size of the infant. Two of the patients who died were delivered vaginally, through greatly damaged passages, and developed what is generally termed a low grade infection, that is, a local infection which gradually spread through the pelvis, the patients dying some weeks after delivery. He regretted that, in these two cases, he had not done a Caesarean hysterectomy, which would have provided much more adequate drainage.

He thought that the cause of failed forceps was, primarily, the complete lack of careful examination, which should precede any attempt at vaginal delivery, and perhaps, a very considerable lack of imagination on the part of the operator.

Dr. J. S. QUIN said that the thanks of the Section were due to Dr. Falkiner for having classified cases of failed forceps so very ably. He never could understand why people took the risk and the trouble of applying forceps when it was so very much easier to do nothing. Nobody of course was to blame for putting on forceps providing that the indications for the application of forceps were fulfilled. He asked Dr. Falkiner if he thought it was worth while taking cultures in these cases, or if he considered that it was better to treat straight away.

Dr. O'DONEL BROWNE said that he thought the blame for cases of failed forceps had to be shared by those who taught obstetrics as well as by those who practised the art. He had seen only two cases. The first patient was a primigravida at term. She was in the first stage of labour and the head was very high. There was no indication at all to deliver her. Forceps had been applied without rupture of the membranes. In the second case there was a complete tear of the perineum.

Dr. T. M. HEALY said that the skull which Dr. Falkiner had shown should be mounted and kept permanently as an exhibit. A picture shown to a class of students was, he thought, very much more impressive than any words of a teacher could be. He referred to the great importance of carefully examining every case, and said that most examinations were made with two fingers. No diagnosis could be made in this way. Either half the hand or the whole hand should be put into the vagina.

Dr. FALKINER, in replying, said that in his case he could hardly believe that such damage could have been done without the use of the old-fashioned forceps. It was very unusual even in a failed forceps case to produce a fracture of the skull. He thought it was time that the term 'low grade infection' ceased to be used. When a case of failed forceps was met with, chemotherapy was in his opinion absolutely indicated, even though it might not be successful.

Mr. F. MORRIN read

NOTES ON A CASE OF ENDOMETRITIS CAUSING INTESTINAL OBSTRUCTION.